

REPORT DOCUMENTATION PAGE			<i>Form Approved</i> <i>OMB No. 0704-0188</i>	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.				
1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE 21 May 98	3. REPORT TYPE AND DATES COVERED	
4. TITLE AND SUBTITLE EFFECTS OF HMG-COA REDUCTASE INHIBITOR THERAPY ON LDL CHOLESTEROL BLOOD LEVELS IN HYPERLIPIDEMIA: A LONGITUDINAL RETROSPECTIVE ANALYSIS USING A DEPARTMENT OF DEFENSE			5. FUNDING NUMBERS	
6. AUTHOR(S) Cynthia Leah Lee-Ziegler				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) The University of Texas at Austin			8. PERFORMING ORGANIZATION REPORT NUMBER 98-001D	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) THE DEPARTMENT OF THE AIR FORCE AFIT/CIA, BLDG 125 2950 P STREET WPAFB OH 45433			10. SPONSORING/MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION AVAILABILITY STATEMENT Unlimited distribution In Accordance With AFI 35-205/AFIT Sup 1			12b. DISTRIBUTION CODE	
13. ABSTRACT (Maximum 200 words) <div style="text-align: center; font-size: 2em; font-weight: bold; transform: rotate(-10deg);">19980527 037</div> <div style="text-align: center; border: 1px solid black; padding: 5px; transform: rotate(-10deg); font-weight: bold;">DTIC QUALITY INSPECTED 2</div>				
14. SUBJECT TERMS			15. NUMBER OF PAGES 205	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT	

Copyright
by
Cynthia Leah Lee-Ziegler
1998

**EFFECTS OF HMG-COA REDUCTASE INHIBITOR
THERAPY ON LDL CHOLESTEROL BLOOD LEVELS IN
HYPERLIPIDEMIA: A LONGITUDINAL RETROSPECTIVE
ANALYSIS USING A DEPARTMENT OF DEFENSE
INTEGRATED DATABASE**

by

Cynthia Leah Lee-Ziegler, BS, MA

Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

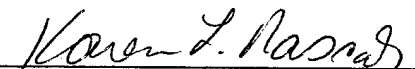
Doctor of Philosophy

The University of Texas at Austin

May 1998

**EFFECTS OF HMG-COA REDUCTASE INHIBITOR
THERAPY ON LDL CHOLESTEROL BLOOD LEVELS IN
HYPERLIPIDEMIA: A LONGITUDINAL RETROSPECTIVE
ANALYSIS USING A DEPARTMENT OF DEFENSE
INTEGRATED DATABASE**

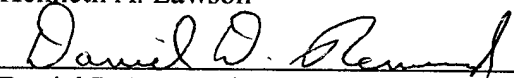
**Approved by
Dissertation Committee:**



Karen L. Rascati, Supervisor



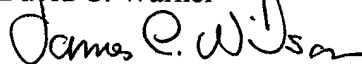
Kenneth A. Lawson



Daniel D. Remund



David C. Warner



James P. Wilson

Dedication

I would like to dedicate this dissertation to my husband, James F. (Skip) Lee, Jr.
Without his loving support and belief in the importance of what I was doing, I
would have found the entire process more difficult if not impossible.

Acknowledgments

I wish to acknowledge my supervisor, Dr. Karen L. Rascati, for her tireless dedication to duty and guidance in directing me through the dissertation process. Her patience and attention to detail have been invaluable.

I wish to thank my entire committee, Dr. Kenneth A. Lawson, Col. Daniel D. Remund, Dr. David C. Warner, and Dr. James P. Wilson for giving me their time and insightful comments in helping to shape this dissertation.

Dr. Robert Talbert served as a clinical consultant, which I wish to thank him for. Maj. Robert Berkheiser served as military consultant and helped guide me through the red tape I encountered. I thank him for that.

For computer assistance and guidance, I would like to thank SFC Thomas Bolinger, Ms. RuLyn Bohn, and Mr. Richard Wahls. Without their help, the data would never have been collected.

**EFFECTS OF HMG-COA REDUCTASE INHIBITOR
THERAPY ON LDL CHOLESTEROL BLOOD LEVELS IN
HYPERLIPIDEMIA: A LONGITUDINAL RETROSPECTIVE
ANALYSIS USING A DEPARTMENT OF DEFENSE
INTEGRATED DATABASE**

Publication No. _____

Cynthia Leah Lee-Ziegler, Ph.D.

The University of Texas at Austin, 1998

Supervisor: Karen L. Rascati

Annual lipid-lowering therapy costs the Department of Defense (DoD) in excess of \$40 million. In 1995, a new computer system was implemented nationwide to assist in tracking medical utilization in addition to performing general operations. Pharmacy, laboratory, and patient administration records were integrated. The purpose of this study was to investigate the five currently marketed HMG-CoA reductase inhibitors (statins) in the military beneficiary population served by this computer system in a selected area. The computer records of patients receiving statin therapy between February 1996 and April 1998 were retrospectively examined: (1) to determine if statin therapy achieved reductions in low-density lipoprotein (LDL) cholesterol levels similar to those

seen in clinical trials; (2) to determine if there were any differences between the five statins in the LDL reductions observed; and (3) to compare the cost-effectiveness of the five statins by using annual estimated treatment costs per one percent reduction in LDL. The perspective for the cost-effectiveness analyses was that of the military. An original sample of 4436 patients resulted in 289 final subjects meeting the criteria of being new statin users and having at least one pre-treatment and post-treatment LDL value on file. As the majority of patients received one particular statin, few comparisons could be conducted. Observed reductions in LDL for patients taking pravastatin were less than predicted by clinical trials, but with 95 percent confidence intervals, approached the predicted values. Patients who had pravastatin listed as the last statin fill had a larger reduction in LDL levels and lower estimated annual treatment costs when compared to patients who had simvastatin listed as the last statin fill. Other comparisons could not be conducted. The advantages and caveats of working with the DoD Composite Health Care System (CHCS) computer system are discussed. This exploratory study yielded ideas for future work.

Table of Contents

LIST OF TABLES.....	xii
CHAPTER ONE - INTRODUCTION.....	1
SECTION I - General Background Information on Hyperlipidemia	9
ATHEROSCLEROSIS	9
OTHER CAUSES OF DYSLIPIDEMIA.....	10
HYPERLIPIDEMIA TREATMENT STRATEGIES	11
COMPLIANCE ISSUES	14
SECTION II - Review of Studies Examining Hyperlipidemia	
Treatment	15
CLINICAL TRIALS - CLINICAL ENDPOINTS.....	16
STATIN-SPECIFIC CLINICAL TRIALS	27
CLINICAL TRIALS/ARTICLES ADDRESSING	
EPIDEMIOLOGIC OR COST ISSUES	
PERTINENT TO HYPERLIPIDEMIA	31
SECTION III - Computer Databases.....	35
ADVANTAGES	35
DISADVANTAGES.....	36
SECTION IV - Rationale for the Study	37
SECTION V - Purpose, Objectives, and Hypotheses.....	39
HYPOTHESES.....	40
REFERENCES.....	41

CHAPTER TWO - METHODOLOGY	66
DATA SOURCE	66
STUDY POPULATION	66
STUDY DESIGN	71
DATA COLLECTION	71
DATA ANALYSIS	76
Demographic Information	76
Objective One	76
Objective Two	78
Objective Three	79
REFERENCES	81
 CHAPTER THREE - RESULTS	 83
ELIMINATION PROCESS	83
DEMOGRAPHIC INFORMATION FOR SUBJECTS NOT MEETING SELECTION CRITERIA VS FINAL STUDY SUBJECTS	86
OBJECTIVE ONE	87
Initial Drug and Mean % LDL Reduction	88
Initial Drug and % LDL Reduction Between Baseline and Last Recorded LDL	92
Final Drug and Mean % LDL Reduction	95
Final Drug and % LDL Reduction Between Baseline and Last Recorded LDL	98
OBJECTIVE TWO	101
Initial Drug as Classification	101
Final Drug as Classification	105

OBJECTIVE THREE.....	110
Initial Drug/Dose as Classification.....	111
Initial Drug Alone as Classification.....	117
Final Drug/Dose as Classification.....	120
Final Drug Alone as Classification.....	127
Cost-Effectiveness Ratios.....	129
Initial Drug as Classification - Overall Sample	130
Initial Drug as Classification - Primary Prevention	133
Initial Drug as Classification - Secondary Prevention	135
Summary - Initial Drug.....	137
Final Drug as Classification- Sample Overall.....	141
Final Drug as Classification- Primary Prevention.....	145
Final Drug as Classification - Secondary Prevention.....	149
Final Drug as Classifier - Summary	153
Sensitivity Analyses.....	157
SUMMARY.....	159
REFERENCES.....	160

CHAPTER FOUR - DISCUSSION AND CONCLUSIONS..... 161

OVERVIEW.....	162
LIMITATIONS OF STUDY.....	168
OBJECTIVE ONE.....	169
OBJECTIVE TWO.....	172
OBJECTIVE THREE.....	173
SENSITIVITY ANALYSIS.....	176
COMPOSITE HEALTH CARE SYSTEM.....	176
OTHER COMMENTS	178

SUGGESTIONS FOR FURTHER STUDY	179
CONCLUSION.....	180
REFERENCES.....	181
BIBLIOGRAPHY.....	182
VITA.....	205

List of Tables

Table 2.1	CHD Risk Factors Other Than LDL.....	69
Table 2.2	Treatment Goals, Based on NCEP Guidelines.....	70
Table 3.1	Patient Demographics	86
Table 3.2	Predicted and Observed Mean % LDL Reduction - Using Initial Drug/Dosing Regimen and Mean Overall % LDL Reduction.....	90
Table 3.3	Predicted and Observed Mean % LDL Reduction - Using Initial Drug and Mean Overall % LDL Reduction.....	91
Table 3.4	Predicted and Observed Mean % Reduction - Using Initial Drug/Dosing Regimen and % LDL Reduction Between Baseline and Last Recorded LDL.....	93
Table 3.5	Predicted and Observed Mean % LDL Reduction - Using Initial Drug and % LDL Reduction Between Baseline and Last Recorded LDL	94
Table 3.6	Predicted and Observed Mean % LDL Reduction - Final Drug/Dosing and Mean Overall % LDL Reduction	96
Table 3.7	Predicted and Observed Mean % LDL Reduction - Using Final Drug and Mean Overall % LDL Reduction.....	97
Table 3.8	Predicted and Observed Mean % LDL Reduction - Final Drug/Dosing and % LDL Baseline/Last LDL.....	99

Table 3.9	Predicted and Observed Mean % LDL Reduction - Using Final Drug and % LDL Reduction Between Baseline and Last Recorded LDL	100
Table 3.10	Observed Changes in LDL Cholesterol Levels - Sample Overall Using - Initial Drug Prescribed.....	102
Table 3.11	Observed Changes in LDL Cholesterol Levels - Primary Prevention - Using Initial Drug Prescribed	103
Table 3.12	Observed Changes in LDL Cholesterol Levels - Secondary Prevention - Using Initial Drug Prescribed	104
Table 3.13	Observed Changes in LDL Cholesterol Levels - Sample Overall - Using Final Drug Prescribed	106
Table 3.14	Observed Changes in LDL Cholesterol Levels - Primary Prevention - Using Final Drug Prescribed.....	108
Table 3.15	Observed Changes in LDL Cholesterol Levels - Secondary Prevention - Using Final Drug Prescribed.....	109
Table 3.16	Annual Cost Estimates of Treatment - Sample Overall Using Initial Drug/Dosing Regimen and Mean Cost.....	112
Table 3.17	Annual Cost Estimates of Treatment - Primary Prevention Using Initial Drug/Dosing and Mean Costs.....	114
Table 3.18	Annual Cost Estimates of Treatment - Secondary Prevention Using Initial Drug/Dosing and Mean Costs	116
Table 3.19	Annual Cost Estimates of Treatment - Sample Overall Using Initial Drug and Mean Costs	118

Table 3.20	Annual Cost Estimates of Treatment - Primary Prevention Using Initial Drug and Mean Costs	119
Table 3.21	Annual Cost Estimates of Treatment - Secondary Prevention Using Initial Drug and Mean Costs	119
Table 3.22	Annual Cost Estimates of Treatment - Sample Overall Using Final Drug/Dosing Regimen and Mean Costs	122
Table 3.23	Annual Cost Estimates of Treatment - Primary Prevention Using Final Drug/Dosing Regimen and Mean Costs	124
Table 3.24	Annual Cost Estimates of Treatment - Secondary Prevention Using Final Drug/Dosing Regimen and Mean Costs	126
Table 3.25	Annual Cost Estimates of Treatment - Sample Overall Using Final Drug and Mean Costs	127
Table 3.26	Annual Cost Estimates of Treatment - Primary Prevention Using Final Drug and Mean Costs	128
Table 3.27	Annual Cost Estimates of Treatment - Secondary Prevention Using Final Drug and Mean Costs	128
Table 3.28	Cost-Effectiveness (Annual Treatment Costs/% Reduction in LDL) - Sample Overall - Using Initial Drug/Dosing and Mean Overall % LDL Reduction.....	131
Table 3.29	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Sample Overall - Using Initial Drug/Dosing Regimen and % LDL Reduction Between Baseline and Last Recorded LDL.....	132

Table 3.30	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Primary Prevention - Using Initial Drug/Dosing and Mean Overall % LDL Reduction.....	133
Table 3.31	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Primary Prevention - Using Initial Drug/Dosing Regimen and % LDL Reduction Between Baseline and Last Recorded LDL	134
Table 3.32	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Secondary Prevention - Using Initial Drug/Dosing and Mean Overall % LDL Reduction.....	135
Table 3.33	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Secondary Prevention - Using Initial Drug/Dosing Regimen and % LDL Reduction Between Baseline and Last Recorded LDL.....	135
Table 3.34	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Sample Overall - Using Initial Drug and Mean Overall % LDL Reduction	136
Table 3.35	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Sample Overall - Using Initial Drug and % LDL Reduction Between Baseline and Last Recorded LDL.....	138
Table 3.36	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Primary Prevention - Using Initial Drug and Mean Overall % LDL Reduction.....	139
Table 3.37	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Primary Prevention - Using Initial Drug and % LDL Reduction Between Baseline and Last Recorded LDL.....	139

Table 3.38	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Secondary Prevention - Using Initial Drug and Mean Overall % LDL Reduction.....	140
Table 3.39	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Secondary Prevention - Using Initial Drug and % LDL Reduction Between Baseline and Last Recorded LDL.....	140
Table 3.40	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Sample Overall - Using Final Drug/Dosing Regimen and Mean Overall % LDL Reduction.....	142
Table 3.41	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Sample Overall - Using Final Drug/Dosing Regimen and % LDL Reduction Between Baseline and Last Recorded LDL	144
Table 3.42	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Primary Prevention - Using Final Drug/Dosing Regimen and Mean Overall % LDL Reduction.....	146
Table 3.43	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Primary Prevention - Using Final Drug/Dosing Regimen and % LDL Reduction Between Baseline and Last Recorded LDL.....	148
Table 3.44	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Secondary Prevention - Using Final Drug/Dosing Regimen and Mean Overall % LDL Reduction.....	150
Table 3.45	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Secondary Prevention - Using Final Drug/Dosing Regimen and % LDL Reduction Between Baseline and Last Recorded LDL.....	152

Table 3.46	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Sample Overall - Using Final Drug and Mean Overall % LDL Reduction	154
Table 3.47	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Sample Overall - Using Final Drug and % LDL Reduction Between Baseline and Last Recorded LDL	154
Table 3.48	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Primary Prevention - Using Final Drug and Mean Overall % LDL Reduction	155
Table 3.49	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Primary Prevention - Using Final Drug and % LDL Reduction Between Baseline and Last Recorded LDL	155
Table 3.50	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Secondary Prevention - Using Final Drug and Mean Overall % LDL Reduction	156
Table 3.51	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Secondary Prevention - Using Final Drug and % LDL Reduction Between Baseline and Last Recorded LDL	156
Table 3.52	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Pravastatin (N = 238) as Final Drug	158
Table 3.53	Cost-Effectiveness (Annual Treatment Costs/% Reduc. in LDL) - Simvastatin (N = 38) as Final Drug	158

CHAPTER ONE

INTRODUCTION

The author of a recent commentary asserts "The future of pharmacoeconomics lies in meeting the needs of decision makers."¹ The Congressional Budget Office forecasted that, by the year 2000, American healthcare expenditures will be \$1.7 trillion, representing 18 percent of the gross domestic product (GDP).² In 1984, coronary heart disease (CHD) was the major cause of death and disability in the United States as well as in other industrialized nations. In 1995, despite public health initiatives, cardiovascular disease still remained the leading killer in Western industrialized nations.³ In 1996, it was estimated that coronary artery disease (CAD) had directly touched the lives of over 13 million Americans, at an annual cost in excess of \$90 billion. These costs include direct medical costs, non-medical costs, and lost productivity costs which are consequences of CAD. Each year CAD causes 500,000 deaths, while other vascular disease patients account for not only 50 percent of all myocardial infarctions (MIs) but also 70 percent of all CAD deaths.^{4,5} Thus, CAD is the leading cause of death for *all* American men and women in any given year. With healthcare, in general, and cardiovascular disease, more specifically, representing such a significant portion of the GDP, medical decision makers are keenly interested in getting accurate and timely information to assist them in making appropriate decisions on where best to spend/invest scarce resources.

A brief discussion of what is meant by the phrase "healthcare costs" is in order. The average consumer may view costs just as money that comes out of his or her own pocket, such as co-payments or the cost of prescriptions at the drug store. A third-party payer, such as an insurance company, may view these costs solely as the claims for billed medical services. An employer may view these costs as the portion of premiums that must be paid on behalf of employees. The healthcare provider, such as a physician, hospital, pharmacist, or health maintenance organization (HMO) may view these costs as labor, materials (such as drugs), overhead, bad debt, and so on.

In general, healthcare costs can be broken down into four broad categories: (1) medical costs (those costs used directly in treating the illness or condition, such as billable expenses for hospital care, physician fees, or medications); (2) non-medical costs (those costs associated with treating the illness or condition but not directly provided by a healthcare practitioner, such as non-reimbursable expenses for transportation to receive treatment, family out-of-pocket expenses during the treatment such as lodging costs to stay near an out-of-town treatment facility, or hiring someone to help around the home due to family illness); (3) indirect costs (also known as lost productivity due to the illness or condition); and (4) intangible costs (or the pain and suffering associated with the illness or condition).⁶ In the examples given in the preceding paragraph, many of these categories of costs were addressed.

At the present time, the fourth type of cost has not been fully quantified as there is disagreement on how best to attach monetary values to these costs. Attempts have been made to develop measurement units such as the quality

adjusted life year (QALY) or healthy year equivalent (HYE), but none have been universally accepted as of yet.⁷ Pharmacoeconomics uses outcome measurements in an attempt to analyze economic consequences/concerns as well as clinical and humanistic concerns to arrive at answers for healthcare decision-making.² It is specifically related to the impacts that drugs and drug therapies will have or are having on medical care in general. It is not easy to recognize which outcomes are appropriate to measure, to be able to accurately measure them, and then to be able to analyze the findings to produce meaningful results.

In 1961, a report from the Heart Disease Epidemiology Study, Framingham, Massachusetts, discussed "three characteristics believed to be associated with proneness to the development of CHD": (1) "elevated serum cholesterol levels;" (2) "hypertension;" and (3) "the electrocardiographic pattern of left ventricular hypertrophy."⁸ More recently, the accepted risk factors for cardiovascular disease have been expanded into two broad categories: those factors that cannot be altered, such as age, gender, and family history; and those that can be altered, such as cigarette smoking, obesity, hypertension, physical inactivity, diabetes mellitus, cholesterol, elevated low-density lipoprotein (LDL) cholesterol, and reduced high-density lipoprotein (HDL) cholesterol.⁹

In 1987, the National Cholesterol Education Program's (NCEP's) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults was charged with considering the available evidence on CHD and high serum cholesterol, identifying pertinent issues, and developing guidelines for physicians and other healthcare providers. Their findings identified elevated LDL levels as "causally related and a major determinant of increased risk of CHD."¹⁰

The panel indicated that, as such, LDL levels should be targeted as one of the primary goals of cholesterol-lowering efforts. In their update article published in 1993,¹¹ LDL levels continued to be identified as the primary target for cholesterol-lowering therapy, along with emphasis on dietary therapy as the first line of treatment, with drug therapy being reserved for those considered to be at high risk for CHD.

Risk factors for CHD were further stratified into positive or negative. Positive risk factors included being a male ≥ 45 years of age, being a female ≥ 55 years of age (or premature menopause without estrogen replacement therapy), having a family history of premature CHD, being a current cigarette smoker, having hypertension (or blood pressure $\geq 140/90$ mm Hg, or taking antihypertensive medication), having low HDL cholesterol (< 35 mg/dl or 0.9 mmol/L), or having diabetes mellitus. The only negative risk factor was having high HDL cholesterol (≥ 60 mg/dl or 1.6 mmol/L). The LDL cholesterol level is used in determining which treatment approach is appropriate for the individual patient. Those patients with clinically established CHD are considered for dietary treatment if their fasting LDL level is > 100 mg/dl (2.6 mmol/L), or for drug treatment if the LDL level is ≥ 130 mg/dl (3.4 mmol/L). Those patients without clinically established CHD but who have two or more of the aforementioned risk factors are recommended for dietary therapy if their fasting LDL level is ≥ 130 mg/dl (3.4 mmol/L), or for drug treatment if the LDL level is ≥ 160 mg/dl (4.1 mmol/L). Those without CHD and having less than two of the risk factors should begin dietary therapy if their fasting LDL level is ≥ 160 mg/dl (4.1 mmol/L), or drug treatment if the LDL level is ≥ 190 mg/dl (4.9 mmol/L).

Young adult men and premenopausal women are considered to be at relatively low risk of CHD even with moderately high LDL levels (160-220 mg/dl or 4.1-5.7 mmol/L) and are not usually considered eligible for drug therapy until their LDL levels exceed 220 mg/dl (5.7 mmol/L). The NCEP's guideline uses treatment goals of lowered LDL level. Those with CHD or other atherosclerotic diseases have an LDL goal of ≤ 100 mg/dl (2.6 mmol/L). Those without CHD but with two or more risk factors have an LDL goal of < 130 mg/dl (3.4 mmol/L). And, finally, those without CHD and less than two risk factors have an LDL goal of < 160 mg/dl (4.1 mmol/L).

The issue of "the" most appropriate endpoint for cholesterol-lowering therapy has been debated in the literature. Some authors support the NCEP's viewpoint that LDL lowering can serve as the endpoint, with decreased total mortality and morbidity in CHD, myocardial infarction, CAD, and stroke being inferred from previous clinical trials.¹²⁻¹⁴ Other authors take the viewpoint that there still remain people in clinical trials who receive treatment, achieve significantly lowered LDL levels, yet still have a clinical event, indicating that lowered LDL levels are not the only factor to consider.¹⁵⁻¹⁷ Possible explanations for these conflicting viewpoints include the fact that medical knowledge and technology have increased dramatically since many of the early trials were conducted as well as the discovery that atherogenesis is not dependent solely on cholesterol or LDL.¹⁸⁻²²

The earliest cholesterol-lowering trials, using the cutting edge therapy of the time, concentrated on altering diet and treating primarily with clofibrate, cholestyramine, nicotinic acid, fibric acid, colestipol, neomycin, estrogen,

dextrothyroxine, gemfibrozil, or a combination of these.²³ In 1987, the first of a new drug class was released in the United States. Instead of inhibiting intestinal cholesterol absorption, acting as bile acid sequestrants, decreasing very-low-density lipoproteins (VLDL), or increasing lipoprotein lipase activity, these drugs competitively inhibit the rate-limiting enzyme in cholesterol biosynthesis (3-hydroxy-3-methylglutaryl-coenzyme A reductase).^{24,25} These drugs have been highly effective in lowering LDL cholesterol and are generally better tolerated than the earlier classes of drugs. It is important to remember that all drug therapy does not replace diet therapy but is an adjunct to it.¹¹ Treatment is arbitrarily divided into primary prevention (to prevent development of clinical cardiovascular symptoms in those not already diagnosed as such) and secondary prevention (to prevent further complications or worsening of symptoms in those with clinically established CHD or other atherosclerotic disease). Again, the treatment approach is based on LDL levels and risk factors. As the atherosclerotic process is becoming recognized as a life-long process, the differentiation between primary and secondary prevention is often subjective. Numerous clinical trials have been undertaken over the past several decades to explore the various treatment regimens for hypercholesterolemia along with the corresponding outcomes. The earlier trials tended to measure total cholesterol levels instead of LDL levels. Most of these early trials are discussed in more detail later in this paper and the reader is referred to the following sections.

The issue of where to find the appropriate outcome (the clinical endpoint) must be addressed next. There are two major categories of research listed by Strom (1994)²⁶ - hypothesis-generating studies and hypothesis-strengthening

studies. These studies can be prospective or retrospective in nature. They can be cohort studies or case-control studies. They can be of a randomized clinical trial or post-marketing surveillance design. They can use existing databases or obtain the necessary data through creation of original measurement instruments. The possibilities are restricted only by the researcher's imagination and time/money/ethical constraints.

As the researcher for this particular study is an Air Force officer, the logical source for research data would seem to be that generated by the military. In 1995, a new and integrated computer system, the Composite Health Care System (CHCS) computer system, was implemented nation-wide in military treatment facilities (MTFs). This system linked up pharmacy, laboratory, radiology, and patient administration records, replacing the previous stand-alone systems. Although each MTF is still a stand-alone CHCS system, in many of the larger metropolitan areas with multiple MTFs, these systems are linked into one common CHCS system. Such is the case in San Antonio, Texas, where four Air Force MTFs and one Army MTF share a common CHCS system. This provides the opportunity to conveniently analyze medical data from hundreds of thousands of military medical beneficiaries. Although no analyses using this specific database are published, at least two studies have used the Uniformed Services Prescription Database Project (USPDP) data, which consists of a summary of data reported by each MTF to the Pharmacoeconomic Center (PEC) located at Fort San Houston, in San Antonio, Texas.²⁷

According to the PEC Update of October 16, 1995,²⁸ the military spent approximately \$40 million in fiscal year (FY) 1993 on lipid lowering drugs. That

same issue also published guidelines for the management of hyperlipidemia based on the recommendations of NCEP. As of November 1997, these guidelines were being updated to reflect the use of statins as the treatment of choice, in conjunction with diet and life-style modifications. To date, there has been no published study to evaluate the impact of the 1995 guidelines beyond what could be categorized as annual usage reports. There have been no studies in this population to validate that the projected percent LDL reduction was achieved nor have there been any studies to investigate whether NCEP LDL goals have been attained in either primary or secondary prevention patients. Nor have there been any studies to determine the overall effects of switching thousands of patients stabilized on lovastatin over to pravastatin, which had been selected by the PEC as the formulary statin. Therefore, there exists an economic need for investigation (greater than \$40 million), a clinical need (how are the patients doing from an outcomes measurement perspective), and a unique opportunity to utilize a virtually untapped database. As there was only one other study currently found in the literature where "cost-effectiveness of initial therapy with 3-hydroxy-3-methylglutaryl coenzyme A" (HMG-CoA) "reductase inhibitors to treat hypercholesterolemia in a primary care setting of a managed-care organization"²⁹ was being investigated, the present study should be an original contribution to scholarship.

SECTION I

GENERAL BACKGROUND INFORMATION

ON HYPERLIPIDEMIA

This section discusses the most common causes of dyslipidemia, the present commonly accepted treatment strategies, and a discussion of the impact of patient compliance, or lack thereof, on therapy.

ATHEROSCLEROSIS

Atherosclerosis is known to the lay population as “hardening of the arteries.” In simple terms, it is characterized by deposits of fatty substances, cholesterol, cellular waste products, calcium, and fibrin in the inner lining of an artery.³⁰ A more technical explanation involves oxidized LDL, arterial tissue macrophages, cytokines and growth factors, formation of foam cells, formation of a fatty streak lesion, formation of a fibrous plaque lesion, formation of a complex lesion with a necrotic core, and the ultimate potential for plaque rupture resulting in potential thrombosis and/or infarction.^{19,31,32} As cholesterol is a naturally occurring substance and is necessary for membrane synthesis as well as steroid hormone production and serves as a precursor for vitamin D,³³ it must be transported from the liver, where it is synthesized, through the blood to the

peripheral tissues.³⁴ The lipoprotein that carries the cholesterol from the liver is LDL, which often ends up depositing the cholesterol on arterial walls. The HDL lipoprotein "sweeps" up the cholesterol from the blood stream and transports it back to the liver. It has been estimated that up to 80 percent of the circulating cholesterol in the average human is the result of internal synthesis, which may explain why some of the earlier trials with blocking agents for intestinal cholesterol absorption or bile acid sequestrants had less effect on lowering LDL levels than the later HMG-CoA reductase inhibitors.

OTHER CAUSES OF DYSLIPIDEMIA

Several disease states or genetic abnormalities are known to cause dyslipoproteinemia. Atherosclerosis is a common complication in diabetics, both insulin-dependent (IDDM) and non-insulin-dependent (NIDDM).^{35,36} It is more common for diabetics to have higher serum triglycerides than elevated cholesterol. It has been postulated that diabetics may have genetically altered LDL lipoproteins, resulting in triglycerides being deposited in the arterial walls instead of the more typical cholesterol. It is also proposed that this effect may be more the result of low levels of HDL that are seen frequently with an increase in triglycerides. Hyperinsulinemia and hyperglycemia also have been suspected of being atherosclerotic in their own right. The genetic disorder of familial hypercholesterolemia (occurring in 1 in 500 people in North America and Western Europe) involves mutations in the LDL receptors that are located on the cells that need to take up cholesterol for further processing. These mutations range from receptors that are produced but are unable to transport the LDL

lipoprotein with its incorporated cholesterol into the cell to those that produce no LDL receptors whatsoever.³⁷ In this condition, the dietary cholesterol is never cleared from the blood as it can not enter the cells for further processing and the endogenous biosynthesis of cholesterol continues as there is no intracellular back regulation. Cholesterol levels of 200-400 mg/dl and higher are seen quite commonly in these patients.³⁸ As a result of all the circulating cholesterol, these patients often develop premature coronary artery disease within the first decade of life. They also tend to be subject to other metabolic problems and commonly develop tendon xanthomas.³⁹ Patients with chronic renal failure and hypothyroidism have also been reported to have dyslipidemias. Certain antihypertensive agents have also been implicated in altering blood lipid levels unfavorably and care should be taken when treating hypertensive patients who are also hypercholesterolemic.

HYPERLIPIDEMIA TREATMENT STRATEGIES

The current NCEP guidelines recommend modifying lifestyle choices as a first line therapy in those individuals at risk for cardiovascular problems. These include smoking cessation, weight loss, and increase in exercise levels. Any underlying health condition that might affect lipid levels of cardiovascular complications should also be controlled, such as hypertension, diabetes mellitus, liver or renal problems, thyroid conditions, and encouraging hormone replacement therapy (HRT) in post-menopausal women. If the patient does not achieve adequate lipid control using this approach, the next step is diet

modification, such as those diets recommended by NCEP or the American Heart Association. Failing that, the next step is to add drug therapy to the regimen of lifestyle and diet modification. Drug therapy can consist of a single agent or a combination of agents. Often non-systemic agents are tried first.⁴⁰ These can be agents that inhibit the intestinal absorption of cholesterol, such as Olestra®, or the bile acid sequestrants or resins, such as cholestyramine or colestipol. Systemic agents can act in the following ways: (1) to inhibit cholesterol biosynthesis, such as the HMG-CoA reductase inhibitors (statins); (2) to decrease the production of very low-density lipoprotein (VLDL), such as nicotinic acid; or (3) to increase the activity of lipoprotein lipase, such as the fibric acid derivatives (gemfibrozil or bezafibrate).⁴¹

Often treatment choice will depend on which specific type of lipoprotein is targeted for modification. Those agents that predominantly lower LDL cholesterol include the statins and the bile acid sequestrants. Those that predominantly lower triglycerides are nicotinic acid and the fibric acid derivatives. People with familial hypercholesterolemia, characterized by a decrease in the number of functioning LDL receptors, usually are treated with combination therapy. Statins and bile acid sequestrants or nicotinic acid and a bile acid sequestrant are the most common treatment approaches. Those with defective apolipoprotein (apo) B-100, caused by failure of the LDL receptor to recognize and bind with LDL, usually are treated with a statin or nicotinic acid. Polygenic hypercholesterolemia, possibly caused by reduced LDL receptor function, may be treated with statins, bile acid sequestrants, or nicotinic acid. Familial combined hyperlipidemia, most likely caused by overproduction of apo

B-100, may be treated with nicotinic acid, fibric acid derivatives (but only with caution in the elderly, obese, or diabetes mellitus patient), statins, or a combination of statin and fibric acid derivative (but only with caution and close monitoring). Familial dysbeta-lipoproteinemia, characterized by increased total cholesterol and triglycerides, should be treated with fibric acid derivatives (especially clofibrate), nicotinic acid (but this may cause problems with glucose tolerance in diabetic patients), or statins. Familial endogenous hypertriglyceridemia and/or familial mixed hypertriglyceridemia, due to increased VLDL levels, respond to nicotinic acid and fibric acid derivatives. Familial chylomicronemia is not treated by drugs. A combination of diet, weight control, and avoidance of alcohol is the preferred therapy here.

Drug therapy is not recommended by the NCEP for primary hypoalphalipoproteinemia, which is characterized by low high-density lipoprotein (HDL) levels. Despite this recommendation, nicotinic acid and fibric acid derivatives have been used in this condition. Diabetics with dyslipidemias have been treated with fibric acid derivatives (alone or in combination with a bile acid sequestrant) or with statins. Nicotinic acid tends to increase insulin resistance, hyperglycemia, and hyperinsulinemia, so it is not commonly used in diabetics. Nephrotic syndrome patients with dyslipidemias have been treated with statins (lovastatin seems to be especially effective) and bile acid sequestrants, although adverse triglyceride effects have been seen. Renal or cardiac transplant patients with dyslipidemia have been treated with gemfibrozil. Statin therapy has produced mixed results in these patients with lovastatin causing problems while pravastatin has had beneficial effects. In summary, lipid therapy depends on the

number and type of risk factors present as well as the most likely cause of the dyslipidemia. There is no one "best" drug treatment.

COMPLIANCE ISSUES

Any time treatment for a condition depends on the patient performing some activity, be it taking pills, losing weight, or monitoring blood glucose levels, there is the possibility for noncompliance. McDermott *et al.* (1997)⁴² summed the concept up by stating "...the full benefits of those pharmacological interventions at various stages in the course of coronary artery disease will not be realized if patients are not compliant with prescribed therapies" (in essence, the medication must be taken and taken properly for it to work). Hitchens (1996)⁴³ explains patients may be noncomplaint because of the following: (1) they do not feel sick so they cannot "feel" that the medicine is making them better; (2) they feel they are wasting their money because they do not see results right away; or (3) they may experience side effects. Depending on the regimen they are to follow, patients may have to swallow a "glass of sand" (cholestyramine) several times a day, take a handful of niacin tablets several times a day, or simply take one tablet or capsule a day (statins). Murphy and Coster (1997)⁴⁴ make the following observation: "The gap between current and ideal practice suggests that rates of compliance in long term therapy are about 50 percent regardless of the illness or setting." Since treatment for hyperlipidemia is usually life-long, patient compliance is a definite concern. Fortunately, statins tend to have few side effects as a class when compared to the other therapies. Hitchens (1996)⁴³ lists

the following as annual discontinuation rates for various lipid-lowering drugs: (1) niacin - up to 46 percent; (2) bile acid sequestrants - up to 41 percent; (3) gemfibrozil (fibric acid derivative) - up to 37 percent; and 4) lovastatin (the first statin) - 15 percent. Most of the studies cited in this project used the value of \geq 80 percent compliance as the criterion for being compliant. One advantage to using military beneficiaries as the data source is that the medications are provided free of charge, so the financial barrier to compliance is eliminated (some patients would contend that the non-medical cost, lost productivity cost, and intangible cost of pain and suffering entailed with using MTFs negates this fiscal advantage).

SECTION II

REVIEW OF STUDIES EXAMINING

HYPERLIPIDEMIA TREATMENT

This section reviews studies investigating hyperlipidemia's effect on various clinical endpoints, studies looking at statin-specific clinical trials, and studies looking at costs in pertinent healthcare arenas.

CLINICAL TRIALS - CLINICAL ENDPOINTS

Clinical trials pertaining to lipid-lowering strategies have concentrated on four main endpoints: (1) coronary events, including deaths; (2) mechanical monitoring of the atherosclerotic process (angiography, arteriography, electrocardiogram (EKG), or ultrasound technology); (3) LDL or cholesterol lowering; or (4) stroke events, including deaths. Some of the HMG-CoA reductase inhibitors will be discussed here, although the majority of the trials specifically examining the "statins" will be discussed later.

Numerous clinical trials have used coronary events and/or total coronary morbidity and mortality as their endpoints. Many of these trials measure lipid levels as well. An on-going prospective program is the Prospective Pravastatin Pooling (PPP) Project and the Cholesterol Treatment Trialists (CTT) Collaboration.⁴⁵ This program is undertaking a prospective meta-analysis to avoid "some of the pitfalls of meta-analysis associated with earlier review."⁴⁵

The PPP portion consists of the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, the Coronary and Recurrent Events (CARE) trial, and the West of Scotland Coronary Prevention Study (WOSCOPS) trial. The primary objectives here are to look at total mortality and cause-specific mortality, with respect to pravastatin usage, so that total mortality effects may be estimated for different risk populations. Additionally, the effects of pravastatin on total coronary events within specific subpopulations will be examined: primary versus secondary treatment; the elderly; men and women who also have diabetes; smokers; patients on antihypertensive medications; and classifications

of patients with specific baseline lipid levels (such as those with total cholesterol levels < 213 mg/dl or 5.5 mmol/L). Non-coronary events (fatal and non-fatal) will also be captured so that the effects of pravastatin on cancer, trauma, and stroke can be addressed.

The CTT portion will prospectively register all major ongoing and planned trials of cholesterol treatment prior to knowing the results of each study. These studies must be "randomized, unconfounded comparisons of treatments aimed at lipid-level modification." Most of the trials use an HMG-CoA reductase inhibitor against either placebo or "usual care," although the Veterans Affairs Low HDL Intervention Trial (HIT) uses gemfibrozil as the treatment of interest and the Women's Health Initiative (WHI) looked solely at diet as active treatment. Currently there are 12 trials registered: the Scandinavian Simvastatin Survival Study (4S); the Post-Coronary Artery Bypass Graft Study (Post-CABG); WOSCOPS; CARE; LIPID; Gruppo Italiano per lo Studio dell Sopravivenza nell' Infarto miocardico (GISSI Prevention); Air Force-Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS), Benzaifibrate Infarction Prevention Study (BIP); (HIT); Medical Research Council/British Heart Foundation Heart Protection Study (MRC/BHF); Antihypertensive Lipid Lowering Heart Attack Trial (ALLHAT); and the (WHI). All trials except the ALLHAT and WHI are projected for completion by the year 2000. It is anticipated that over 65,000 patients will ultimately be involved in either the PPP or CTT portions. This should yield more reliable estimates of the effects of cholesterol treatment on each cause-specific mortality as well as coronary mortality effects within the identified subgroups.

Several articles have been published concerning the West of Scotland Coronary Prevention Study (WOSCOPS).⁴⁶⁻⁵⁰ This double-blinded study equally randomized 6595 men between the ages of 45 and 64 years to either pravastatin 40 mg nightly or placebo for 4.9 years. The average baseline cholesterol was 272 mg/dl. The primary endpoints were non-fatal myocardial infarction (MI) or coronary heart disease (CHD) death, as a first event. For study purposes, these two endpoints were combined. The intention-to-treat approach was used for statistical analysis. The combined endpoint was a reduction of non-fatal MI and CHD death of 31 percent (95% CI 17-43%), $p < 0.001$, when pravastatin was compared to placebo. The absolute difference in risk of the combined endpoint between pravastatin and placebo at the five-year point was 2.4 percentage points (5.5% vs. 7.9%, respectively). Nonfatal MI risk reduction was significant at the $p \leq 0.001$ level, regardless of whether the definite cases were considered alone or with the suspected cases. For CHD deaths, there was a 33 percent risk reduction (95% CI 1-55%), $p = 0.042$. This was only true when the definite and suspected cases were combined, due most-likely to the small number of definite cases. Overall, death from all cardiovascular causes yielded a 32 percent risk reduction (95% CI 3-53%), $p = 0.033$. There were 46 strokes (six were fatal) in the pravastatin group and 51 (four fatal) in the placebo group. There were no statistically significant differences between the two groups with respect to cancer, suicide, or trauma. There were 116 patients in the pravastatin group who developed cancers (fatal and non-fatal) as compared with 106 in the placebo group ($p = 0.55$). There were 20 patients in the pravastatin group who reported myalgia, 97 who reported muscle aches, 19 in the placebo group who reported

myalgia, and 102 who reported muscle aches. Liver enzymes and creatinine kinase concentrations were not statistically significant between the two groups. Two-fold differences between those with prior vascular disease (26 cardiac events/1000 patients/year for placebo vs. 18 cardiac events/1000 patients/year for pravastatin) and those without prior vascular disease (15 cardiac events/1000 patients/year vs. 9 cardiac events/1000 patients/year) were noted.⁴⁶

The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study was designed as a randomized, double-blind, placebo-controlled trial being performed in 85 teaching hospitals or provincial base hospitals in Australia and New Zealand.^{51,52} Between April 1990 and September 1992, 11,106 patients were registered, resulting in 9014 final subjects. Baseline cholesterol levels were 155-271 mg/dl (4.0-7.0 mmol/L). Patients received either pravastatin 40 mg nightly or placebo. As of February 1, 1995, 1096 (12.2%) of the patients receiving either treatment had discontinued treatment. Overall compliance was estimated to be approximately 87 percent. The blinded CAD mortality rate for both treatment groups was 1.8 deaths (1.6-2.0) per 100 person years. It is estimated that deaths due to CAD will account for 80 percent of total mortality and that in the control group the CAD death rate would be approximately 2 percent per year after the first 12 months. The trial continues.

The Scandinavian Simvastatin Survival Study (4S) was a randomized, double-blind, study designed to evaluate the effect of cholesterol reduction with simvastatin on mortality and morbidity in hypercholesterolemic patients with angina pectoris or myocardial infarction.⁵³⁻⁵⁶ There were 4444 patients selected for inclusion and they were followed at 94 clinical centers in Scandinavia. The

median follow-up time was 5.4 years, with a range of 4.9-6.3 years. During the study, 438 patients died, 256 (12%) in the placebo group and 182 (8%) in the simvastatin group. The relative risk of total mortality in the simvastatin group was 0.70 (95% CI 0.58-0.85), $p = 0.003$. The relative risk of coronary death in the simvastatin group was 0.58 (95% CI 0.46-0.73). There were no statistically significant differences between the two groups with respect to non-cardiovascular deaths, violent deaths (suicide + trauma), fatal cancers, cerebrovascular deaths, or deaths from other cardiovascular diseases. Numerous secondary endpoints are itemized in the reference section of the article by Kjekshus and Pederson.⁵³

The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), initiated in 1973, looked at 3810 men (age 35-59 years) with elevated plasma cholesterol levels (265 mg/dl or greater). The subjects were to be treated with either cholestyramine resin or placebo (double-blind assignment), and followed for approximately seven years.^{3,57} The primary endpoint for evaluating treatment was the combination of definite CHD death and/or definite non-fatal MI. Additional endpoints included "suspected atherosclerotic CHD death," suspected MI, EKG (as classified by Minnesota Code), enzymes (both diagnostic and equivocal), and other deaths not attributable to CHD. Using the stratified log rank test, the cholestyramine group had a 19 percent (90% CI 3-32%), $p < 0.05$ lower incidence rate of CHD than did the placebo group. The all-cause mortality was reduced only by 7 percent in the cholestyramine group (90% CI -23% to +32%).

In 1973, a random sample of 4637 men (35-64 years old age), 99 percent of whom were of French Canadian descent, was recruited in the Quebec city

metropolitan area for the purpose of gathering prospective evidence for an association between small, dense LDL particles (LDL-PPD) and adverse events.^{58,59} Starting in 1985, the relationship between apoprotein (apo) A-I, apo B levels, and ischemic heart disease (IHD) in 2155 men (aged 45-76 years old and a subset from the original 1973 Quebec Cardiovascular study) was investigated using 5-year survival data from 1985 to 1995. The diagnosis of first IHD event included typical effort angina, coronary insufficiency, non-fatal MI and coronary death. Cox Proportional-Hazards Coefficients, stepwise analysis for the prediction of IHD, and Multivariate Conditional Logistic Analysis were done using seven different models to estimate odds ratios (95% CIs) for these events. Potential confounders, such as diabetes mellitus, medication use, family history of IHD, and systolic blood pressure were adjusted for in determining the odds ratios.

The Multiple Risk Factor Intervention Trial (MRFIT) used diet as the sole lipid-lowering treatment.^{60,61} The conclusions from this study were that there are additive independent relationships between macronutrient intake and blood pressure, independent of dietary sodium, potassium, alcohol, and calorie balance. The authors imply that this contributes “importantly” to the prevention and control of high-normal and high blood pressure and major cardiovascular diseases.

There are a number of review articles that discuss a variety of clinical trials using clinical endpoints of risk of reinfarction, risk of CHD, rate of fatal CHD or non-fatal MI, rate of non-CHD mortality, total mortality, or risk of CAD.⁶²⁻⁶⁹ These reviews will not be discussed here in detail; however, the reader is referred to them if further details are desired. A variety of drug therapies in

addition to dietary modification were used in the trials discussed. The trials varied in duration from several weeks to years. The findings were mixed as to the results of lipid-lowering treatment.

The Familial Atherosclerosis Treatment Study (FATS) used angiographic evidence as the primary endpoint for statin therapy.⁷⁰⁻⁷² Or put another way, the change in the severity of disease in the proximal coronary arteries was assessed by quantitative arteriography and served as a measure of clinical effectiveness. After 2 1/2 years, the average percentage of stenosis increased by 2.1 percentage points with conventional therapy, decreased by 0.7 percentage points in treatment with lovastatin and colestipol, and decreased by 0.9 percentage points in treatment with niacin and colestipol.

The Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) was undertaken to determine whether lovastatin retarded the progression or facilitated the regression of coronary atherosclerosis as assessed by serial quantitative coronary arteriography.^{73,74} This trial looked only at high risk patients and was a retrospective analysis of 313 medically treated patients who had two coronary arteriograms. Coronary events and classification of angina class during the study were also collected. Multivariable analysis indicated that the observed coronary change score between the treatment groups was small (0.04 mm), and is of debatable clinical relevance. The authors state that on a per-patient basis, the active treatment reduced progression of lesions (even without regression elsewhere) by 1/2 to 1/3. They further state that 42 percent of the lovastatin group still had progression of some type. They conclude that lovastatin slows coronary progression and prevents the development of new coronary lesions.

The Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II) trial consisted of 151 coronary patients who were randomized to either placebo or pravastatin and then treated and followed for three years.^{75,76} This trial was initiated in 1987 and used B-mode ultrasonography to quantify intimal-mediated thickness (IMT) of the extracranial carotid arteries as the primary outcome. This study used both men and women who had elevated LDL cholesterol levels. Pravastatin was associated with a 12 percent reduction in the progression rate of the primary outcome measure, but this was not statistically significant ($p = 0.44$). Pravastatin was associated with a 60 percent reduction in clinical CAD events ($p = 0.09$), a 61 percent reduction for the combined endpoint of any coronary event and any death ($p = 0.04$), and an 80 percent reduction in fatal plus non-fatal MI ($p = 0.03$).

The Asymptomatic Carotid Artery Progression Study (ACAPS) used the statins alone or in combination with other agents over a 3-year period in 919 men and women, to evaluate whether the progression of IMT in carotid artery segments was retarded.⁷⁷ As a secondary endpoint, major cardiovascular events were monitored. The authors conclude that this study shows that B-mode ultrasonography is a statistically valid and efficient technique for measuring progression of carotid atherosclerosis, and that even with their limited prespecified power, that the potential preventative effect of statins on major cardiovascular events and all-cause mortality was supported.

The Kuopio Atherosclerosis Prevention Study (KAPS) was a population-based, double-blind trial in the primary prevention of carotid and femoral atherosclerosis using pravastatin 40 mg daily or placebo, for a period of three

years.^{78,79} There was a 45 percent reduction (95% CI 16-69%) in progression in the carotid arteries with pravastatin. When the carotid and femoral segments were combined, there was a 32 percent treatment effect (95% CI 7-53%, $p=0.020$). The number of clinical cardiovascular events was lower for the pravastatin group, but not statistically significant.

The Regression Growth Revaluation Statin Study (REGRESS) was designed to determine the effects of lipid reduction with pravastatin on the progression and regression of coronary atherosclerosis in a broad range of patients.^{80,81} A total of 885 patients in the Netherlands were randomly assigned to study groups: 230 in the percutaneous transluminal coronary angioplasty (PTCA) group; 282 in the coronary artery bypass graft (CABG) group; and 373 to the medical management group. The authors concluded that REGRESS showed a beneficial effect of pravastatin on the primary (angiographically assessed progression and regression of coronary atherosclerosis) and secondary (occurrence of clinical events) endpoints in both coronary and peripheral arteries. They also stated that B-mode ultrasound data cannot be unconditionally used as a substitute for coronary arteriography.

Three other trials using angiography or similar techniques to monitor endpoints were the Multicentre Anti-Atheroma Study (MAAS),⁸² the Harvard Atherosclerosis Reversibility Project (HARP),^{83,84} and the Monitored Atherosclerosis Regression Study (MARS).⁸⁵ Review articles comparing and contrasting these and similar studies are also available.^{18,86-89} These will not be discussed here other than to state that mixed results were found and that as the etiology and course of atherosclerosis continues to be revealed through ongoing

research, new approaches to measuring endpoints should be developed as these studies did not yield definitive findings.

Trials looking specifically at risk of stroke are much less numerous than the other clinical endpoints trials for lipid-lowering therapy. Five articles were found, three of which were review articles.^{14,90-94} The majority of these articles were descriptive in nature or were in the form of post-hoc analysis of trials that reported stroke, although not as the primary endpoint. The trials used statins, diet alone, or other interventions, and reported mixed results. As most of the trials were conducted in men, nothing could be extrapolated to women.

The majority of the clinical trials use either total cholesterol level (in older trials) or LDL level (in more recent trials) as their primary endpoints. It is beyond the scope of this paper to address all these trials. Most of the previously discussed trials also included measurement of these levels at baseline and during the course of the trial. The reader is referred to a selection of the review articles found during the literature review.^{14,95-97} These trials usually showed a reduction in LDL or cholesterol level with a corresponding reduction of CHD, CAD, or other cardiovascular events. The reduction amounts varied depending on the agents used and what other risk factors were present. In general, the statins lowered the LDL levels in the 20-40 percent range, while combination therapy was most effective in those situations where triglycerides were elevated or the hypercholesterolemia was due to an underlying disease state.

Specific trials in special populations will be discussed here briefly, although many more are available in the literature. The Heart and Estrogen/Progestin Replacement Study (HERS) matched hormonal therapy in

women with established coronary disease to determine if the NCEP guideline levels of LDL reduction were attainable.⁹⁸ The Cholesterol and Recurrent Events (CARE) trial matched reduction in CAD events to reduction in cholesterol level.⁹⁹ The Helsinki Heart Study tested the hypothesis that lowering LDL-C and triglyceride (TG) levels and elevating HDL-C levels with gemfibrozil in dyslipidemic men would reduce cardiac events.¹⁰⁰⁻¹⁰¹ The Expanded Clinical Evaluation of Lovastatin (EXCEL) Study was undertaken to clarify the dose-response relation of lovastatin therapy to lipid-modifying efficacy in a mixed population of moderately elevated cholesterol patients.¹⁰²⁻¹⁰⁴ The Systolic Hypertension in the Elderly Program (SHEP) sought to explore the idea that serum lipids remain CHD risk factors in older Americans^{105,106} while the Leiden 85-Plus and Zutphen studies explored similarly elderly representatives in two towns in the Netherlands.¹⁰⁷ The Rancho Bernardo Heart and Chronic Disease Study followed 2360 middle to upper-middle class men and women of a community in southern California from 1984-1994 to study the effects of age, weight change, and covariates on lipid and lipoprotein levels.¹⁰⁸

Ethnic populations were studied in the following four studies. In the Bogalusa Heart Study,^{109,110} biracial children in this Louisiana town were monitored for 15+ years for the effects of dyslipidemia on CAD and other cardiovascular risks. In the San Antonio Family Heart Study (SAFHS),¹¹¹ Mexican Americans in 42 extended families were examined for lifestyle and medical history as well as phenotype assessment for the purpose of proposing genetic factors for cardiovascular risks. The San Luis Valley Diabetes Study¹¹² compared and contrasted plasma levels of various lipid and lipoprotein

components to determine if there were quantitative differences between normoglycemic Hispanics and normoglycemic non-Hispanics in this area of Colorado. One of the goals of the National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study¹¹³ was to collect longitudinal health information stratified by ethnicity, specifically about African-Americans.

None of the trials discussed in this section has definitively answered the question of which is the "best" clinical endpoint or which is the "best" treatment approach. There is no one "best" answer as there are seemingly endless list of "it depends" modifiers to potentially invalidate what is seen in the trials. The best approach appears to be that of the NCEP¹¹ which is to evaluate the cardiac risk factors present and to initiate therapy when indicated.

STATIN-SPECIFIC CLINICAL TRIALS

At the present time, there are five HMG CoA reductase inhibitors available in the United States. They are atorvastatin (Lipitor® by Bristol-Myers Squibb), fluvastatin (Lescol® by Sandoz), lovastatin (Mevacor® by Merck), pravastatin (Pravachol® by Bristol-Myers Squibb), and simvastatin (Zocor® by Merck). Similar to certain antibiotics, the statins can be considered as having "generations" with lovastatin and pravastatin being first generation statins (derived from natural sources through fermentation), simvastatin being a "first-and-a-half"⁴⁰ generation statin (semi-synthetic), fluvastatin being a second generation statin (a racemic synthetic), and atorvastatin being a third generation

statin (a pure enantiomer synthetic). Atorvastatin, fluvastatin, and pravastatin are taken in the active hydroxy-acid form¹¹⁴ while lovastatin and simvastatin are taken as prodrugs, meaning they must be converted into active metabolites in the body.

All the statins work by inhibiting endogenous cholesterol synthesis. This is done by inhibiting the enzyme HMG-CoA reductase which, in turn, impedes mevalonic acid formation, a rate-limiting step in cholesterol synthesis. Because there is less cholesterol within the cell, the theory is that the cell increases the number of LDL-receptors to enable LDL cholesterol to be transported from the plasma into the cell. As a group, statins generally lower LDL cholesterol by 20-40 percent and increase HDL cholesterol (the "good" cholesterol) by 5-10 percent.¹¹⁵ As a group, their adverse effects include headache, GI disturbances, liver enzyme elevation, skin rashes, myopathy with elevated creatinine phosphokinase (CPK), and rhabdomyolysis and acute renal failure in rare instances (especially in patients receiving cyclosporine, gemfibrozil, niacin, erythromycin, clarithromycin, or azithromycin).¹¹⁶ There is some evidence that atorvastatin lowers triglycerides to a greater extent than the other statins, although the exact mechanism of how it does this is still unclear. Lovastatin should be taken with meals to improve its bioavailability, while the rest of the statins do not have this requirement.

A further literature search looking specifically at statins and clinical trials, beyond those trials already discussed, yielded the following results. There were 36 clinical trials investigating a specific statin,¹¹⁷⁻¹⁵² seven clinical trials investigating combination therapy with a statin and another agent,¹⁵³⁻¹⁵⁹ 10

clinical trials investigating statin therapy as compared with another specific lipid-regulating agent,¹⁶⁰⁻¹⁶⁹ and 10 clinical trials that were head-to-head comparisons of a specific statin with one or more other statins.¹⁷⁰⁻¹⁷⁹ There were eight review articles that dealt with specific statins,¹⁸⁰⁻¹⁸⁷ one review of all the statins,¹⁸⁸ two reviews of statin versus statin,^{189,190} and two articles (a review and a commentary) addressing the potential of carcinogenicity of lipid-lowering drugs in general.^{191,192} Four articles were found that addressed the cost-effectiveness of statins or lipid-lowering treatments including statins.¹⁹³⁻¹⁹⁶ Seven other articles were also found that dealt with statin therapy and clinical trials pertaining to them.¹⁹⁷⁻²⁰³

The trials used a variety of methodologies as well as a variety of therapeutic endpoints to look at a variety of treatment modalities. The general consensus of the articles was that the statins were highly effective at reducing LDL levels and were generally well tolerated, although there have been myalgia, elevated liver enzymes, and increased risk of cancer in animal studies. There is some concern that since this class of drugs has only been available to the public in the United States since 1987, the long-term effects are still undetermined. The consensus was also that these agents should be used as an addition to dietary treatment, never as a replacement for diet modification. All the treatment criteria mentioned in the first portion of this report should be followed before initiating statin therapy (such as high risk patients, those with greater than two risk factors, those with prior coronary or cardiovascular events, and those with comorbid conditions).

Some of the statin trials were performed in specific subpopulations of patients. The consensus was that if there is an underlying disease state or environmental concern that can be modified (such as increasing exercise, having good diabetic control, losing weight, or ceasing to smoke), these strategies should be implemented prior to drug therapy if at all possible. Those patients with familial hypercholesterolemia usually will require treatment with another drug in addition to a statin as statins do not exert much effect on triglyceride levels. It was also the consensus that if a therapy failed, it was often better to add a different drug to the regimen instead of just increasing the dose of the present statin. There is a diminishing return in LDL lowering with the higher statin dosing levels. The statins were conventionally viewed as interchangeable with one another, with no real advantage or disadvantage. Atorvastatin, the newest release in the United States, is being touted as having greater triglyceride effects as well as HDL elevation effects. Pravastatin is more lipophilic than the others, which some feel may be an advantage or disadvantage. Several of the drugs are administered as pro-drugs (lovastatin) while others are administered as active drug (pravastatin). All have a significant first pass effect, which is not surprising as the target organ for action is the liver. Usually any liver enzyme elevations gradually return to normal after discontinuation, and are generally seen in only 1-2 percent of all patients.

CLINICAL TRIALS/ARTICLES ADDRESSING EPIDEMIOLOGIC OR COST ISSUES PERTINENT TO HYPERLIPIDEMIA

From the standpoint of using LDL as a surrogate or intermediate endpoint for measuring reduction in coronary events as well as other cardiovascular consequences, the previously discussed trials and articles support this premise for the most part. Although there continues to be debate as to whether LDL level is "the" best predictor for decreased risk of coronary or cardiovascular events, it is generally agreed that there is a corresponding proportional drop in events when the LDL level is lowered. Since "true" endpoints of decreased morbidity and mortality may take decades to manifest, especially in the primary prevention patients, LDL level is considered an appropriate measure of disease progression. In fact, one recent study from Finland investigated the effects of a low saturated fat diet during the first three years of life on preatherosclerotic lesions and lipid levels in general.²⁰⁴ Another study from North America is a longitudinal study of the development of cardiovascular risk factors in children from ages 8 to 18.²⁰⁵ Here total cholesterol levels are being tracked as predictors. The Cardiovascular Risk in Young Finns Study²⁰⁶ monitored a variety of serum lipid levels from 1980-1992 in children and young adults. The Framingham Study was revisited by William B. Kannel²⁰⁷ to determine the relative risk of a variety of coronary problems based on serum cholesterol levels. The National Health and Nutrition Examinations Surveys (NHANES) II (data collected from 1976-1980) and III (data collected from 1988-1991) were analyzed in three articles²⁰⁸⁻²¹⁰ which focused on epidemiologic issues. The effects of socioeconomic status (SES) on cardiovascular risk, including serum total cholesterol levels, were investigated in

the Minnesota Heart Survey.²¹¹ Until more definitive lipoprotein indicators can be discovered along with the laboratory techniques necessary to capture them, monitoring LDL levels seems a reasonable surrogate to measure in clinical trials.

There has been some concern from a monetary point of view that treating every patient who could be eligible for lipid-lowering therapy will be cost-prohibitive. The general consensus was that following the NCEP's guidelines should help avoid this. LaRosa,¹⁸ states: "...the studies of cost effectiveness" in secondary prevention "are fairly consistent in demonstrating that such intervention is not only highly cost effective but even cost saving." He goes on, however, and states: "...the argument" often used against primary prevention is "that too many patients have to be treated to prevent 1 coronary death." Gonzalez (1996)²¹² maintains that "...it appears that therapy with HMG-CoA reductase inhibitors can lower overall health care costs in patients with CHD by decreasing the use of more expensive services" (such as coronary events, hospitalizations, and corrective procedures). From a marketing point of view, when fluvastatin was released to the general public, the pricing strategy was such that both the higher and lower strength dosage forms were identically priced, as well as being much lower than the statins currently on the market. It was not surprising to see that the cost-effectiveness articles at that time tended to pick fluvastatin as the preferred agent.^{5,195}

Studies having cost-effectiveness components have calculated ratios in a number of ways. Jacobson (1996)⁵ estimated cost-effectiveness by annualizing drug costs (only average wholesale acquisition costs were used to represent costs) and then indexing these against effectiveness (reduction in LDL cholesterol),

yielding cost per 1 percent reduction in LDL cholesterol. The author states that “most cost-effectiveness analyses with the statins support the suggestion that drug acquisition costs account for the majority of changes in the cost-effectiveness ratios.”⁵ He also states, “Overall, fluvastatin has the lowest cost per LDL cholesterol reduction.”⁵ Martens *et al.* (1994)¹⁹⁵ estimated cost-effectiveness based on cost per year-of-life saved. They incorporated drug costs (acquisition costs) and monitoring costs into their estimate of annual cost of therapy. They concluded that future head-to-head studies using statins “could provide further evidence that therapy initiated with fluvastatin may be the most cost-effective way to treat” eligible patients.¹⁹⁵

Spearman *et al.* (1997)²⁹ estimated cost-effectiveness using direct medical costs (physician and laboratory costs) and pharmacy costs (charges for statin drugs with discounts, rebates and patient co-pays deducted, and dispensing fees) to represent treatment costs. Effectiveness was represented by percent reduction in LDL cholesterol. They also looked at cost-effectiveness from the patient’s perspective using the above cost estimates and foregone wages (including adverse drug effects and opportunity costs to the patient in addition to lost wages) to depict total costs. Percent reduction in LDL was based on the six-month value after statin initiation. As this study was conducted in a managed care environment, all physician and laboratory costs were considered constant and the only discriminating factor was drug cost. The authors found that, “in every instance, the CE ratio of fluvastatin was less than that of the other... products.”²⁹ Sensitivity analyses were performed using the 25th and 75th percentiles as best case and worst case scenarios.

One interesting prospective study has as its purpose to be "the first direct cost-effectiveness comparison of several agents in the same class" (the statins).¹⁷³ As this study is still in the design stage, no data are yet available. The authors are estimating cost-effectiveness in three ways. The first way is by measuring the cost of treatment per percentage of patients reaching NCEP target LDL goal at any time during the study. The second approach is by measuring the cost per percentage of patients at NCEP target level at the end of the study. The last estimation will be based on the cost per percentage change in the LDL (although the time frame is not specified here). The authors postulate that the statins can be ranked based on effectiveness as follows: atorvastatin > simvastatin > lovastatin > fluvastatin (pravastatin is not addressed in their study). Fluvastatin is described as being "the least effective on a per milligram basis, but the price per tablet is the lowest."¹⁷³ They justify their study by the belief that comparing the actual resource utilization helps to define the true cost of therapy.¹⁷³

Several articles were found that addressed costs and various healthcare scenarios, both specific to hyperlipidemia and to healthcare in general. One article specific to hyperlipidemia quoted cost-effectiveness ratios from \$3,300 to \$15,000 per year of life saved in older men and women treated for secondary prevention with statins.²¹³ Another focused on dietary treatment in Spain and found cost-effectiveness ranges of \$6,270 to \$61,439 per year of life gained for men and \$28,067 to \$171,459 per year of life gained for women.²¹⁴ A third article presented several interesting nomograms for predicting five and ten year risks of a cardiovascular or cerebrovascular event in those with no prior history of such.²¹⁵ An additional article addressing formulary management in a MTF was

also found.²¹⁶ While this article did not specifically deal with cost, it not only provided an overview of how the formulary process works in the MTF environment but also explained why cost-effective prescribing and utilization is critical given the constraints of modern healthcare. This article puts the present research into the realm of practical applicability.

SECTION III

COMPUTER DATABASES

This section will briefly discuss both the advantages and disadvantages of using a large database as the source of research data.

ADVANTAGES

The most obvious advantage to using a large database is that, if it is comprehensive and complete, it will be analogous to "one-stop shopping." Theoretically every data field the researcher needs would be contained in an easily accessible format within the database. Managed care organizations^{217,218} and governmental agencies²¹⁹ have historically maintained large databases, although claims processing and tracking have been the primary roles. Often these populations represented by the databases are required by their healthcare coverage to use specific providers and facilities, which allows for a greater probability that healthcare encounters will be captured in those databases. The large number of subjects available to the researcher in a single location may also

be advantageous as it is more efficient from a time and money standpoint. Large databases facilitate both retrospective²²⁰ or prospective research^{1,221} since past data can be retrieved while prospective data can be accumulated in a concurrent manner. As information technology and management continue to develop, extracting data from these databases should become faster, easier, and more comprehensive, provided the desired information is recorded there in the first place.

DISADVANTAGES

The major disadvantage with databases of any type is that the desired information may not be present or, if present, will be of indeterminate validity. Often databases are not integrated, resulting in piecemeal data collection. Or the data may only be accessible through running reports and then manually analyzing the results. In the words of one author: "...manually extracting" data "from reports that are printed from one database and then reentering the information into another database is time-consuming and inefficient."²²² There is also the potential for selection bias in the study population as only those who have data in the database may be selected. Lack of standardized data entry protocols may also be a concern when using databases.

As computer technology expands into all arenas of healthcare, the concern for patient privacy and confidentiality has become more common. As the move towards a "paperless" medical chart continues, an increasing amount of very sensitive and potentially harmful information is being stored in these databases.

The concern is that this information is not being adequately safe-guarded against access and use by unauthorized individuals and organizations.²²³ This matter is essentially a question of how to balance the personal privacy of the individual against the societal benefits derived from accessing and utilizing the information in question. Most legislation addressing the privacy issue is generated at the state level and, as such, varies greatly. As this study is being conducted in the military environment, unique privacy regulations are in place to protect patient confidentiality. No patient identifying characteristics may be released without patient consent. Any data analysis that is published or leaves the confines of the MTF must be done in an aggregate form or with all patient specific information deleted. As patient identification numbers are variations of social security numbers, it is especially critical that this information not be released to unauthorized persons or organizations.

SECTION IV

RATIONALE FOR THE STUDY

Dyslipidemias in the industrialized nations remain the number one killer despite public health initiatives to control them through dietary modifications. The NCEP has established specific treatment guidelines based on risk factors and LDL levels as criteria for treatment protocols. The statins, although only in clinical practice for approximately 10 years, have been shown through clinical

trials to be effective in reducing serum lipid levels and effecting a corresponding reduction in coronary and cardiovascular events. The use of LDL levels as a surrogate endpoint is supported by the literature.

The dissertation will tie statin utilization with LDL level in the selected DoD database using a retrospective longitudinal approach to evaluate effectiveness (how well the statins work in "real-world" practice settings) as compared to efficacy (how well they work under ideal conditions such as randomized control trials). This approach is supported by the literature, as discussed previously. With the implementation of the Composite Health Care System (CHCS) computer system, the pharmacy database and the laboratory databases can be accessed from the same terminal. For the purposes of the dissertation, it is assumed that all patients have followed and continue to follow the NCEP guidelines concerning dietary modification at the same level. It is also assumed that as these drugs tend to be expensive, retailing for between \$50 to \$80 per month, the prescription utilization records should be fairly complete (the barrier to acquisition due to monetary expense having been eliminated).

Since the management of hyperlipidemia cost the DoD \$40 million annually in FY93 for lipid-lowering agents alone, this is an issue of importance. Data collection and analysis will provide valuable information to military decision-makers that is not otherwise readily available now. When useful findings can be demonstrated by utilizing the present integrated CHCS database, this will allow future research or analysis projects to be more fully supported and encouraged.

SECTION V

PURPOSE, OBJECTIVES, AND HYPOTHESES

The overall purpose of this study is to examine patient outcomes, using LDL cholesterol blood levels as surrogates for long-term cardiovascular effects, for a select population of military beneficiaries in the San Antonio, Texas, catchment area who are receiving HMG-CoA reductase inhibitor (statin) therapy for hyperlipidemia. An additional aim for this study is to use the integrated CHCS database as the source for all data collected as it is a virtually unexplored resource.

The specific objectives of the study are:

1. to determine whether LDL cholesterol blood levels are being lowered by statin therapy in the actual-use setting of military beneficiaries in the San Antonio CHCS population as predicted by the October 1995 PEC guidelines and by clinical trials;
2. to determine whether there are any differences in this population in percent LDL reduction between the specific statin drugs used; and
3. to compare the cost-effectiveness by calculating treatment cost (medication costs, office visit costs, and laboratory costs) per percent reduction in LDL cholesterol.

For each of the above objectives, data from primary and secondary patients will also be assessed separately.

HYPOTHESES

1. There is no difference between LDL level reduction due to statin therapy in the military beneficiary population in San Antonio, Texas, and that predicted by the 1995 PEC hyperlipidemia treatment guidelines or that observed in clinical trials using statin therapy (to be calculated individually by treatment/dosing regimen and by specific statin class).
2. There are no differences between the five statins (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin) in the mean percent reduction in LDL.
3. There are no differences in the cost-effectiveness between the five statins.

REFERENCES

1. Paul C. Langley, The Future of Pharmacoeconomics: A Commentary. *Clinical Therapeutics* 1997;19(4):762-769.
2. J. Lyle Bootman, Raymond J. Townsend, and William F. McGhan, Chapter 1: Introduction to Pharmacoeconomics. Principles of Pharmacoeconomics, Second Edition, J. Lyle Bootman, Raymond J. Townsend, and William F. McGhan, eds., Harvey Whitney Books Company, Cincinnati, OH, c1996:5-18.
3. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial Results: 1. Reduction in Incidence of Coronary Heart Disease. *Journal of the American Medical Association* 1984; 251(3):351-364.
4. Patricia A. Peyser, Genetic Epidemiology of Coronary Artery Disease. *Epidemiologic Reviews* 1997; 19(1):80-90.
5. Terry A. Jacobson, Cost-Effectiveness of 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitor Therapy in the Managed Care Era. *American Journal of Cardiology* 1996; 78(6A):32-41.
6. Lon N. Larson, Chapter 3: Cost Determination and Analysis. Principles of Pharmacoeconomics, Second Edition, J. Lyle Bootman, Raymond J. Townsend, and William F. McGhan, eds., Harvey Whitney Books Company, Cincinnati, OH, c1996:44-59.
7. Stephen J. Coons and Robert M. Kaplan, Chapter 6: Cost-Utility Analysis. Principles of Pharmacoeconomics, Second Edition, J. Lyle Bootman, Raymond J. Townsend, and William F. McGhan, eds., Harvey Whitney Books Company, Cincinnati, OH, c1996:102-126.
8. William B. Kannel, et al., Factors of Risk in the Development of Coronary Heart Disease - Six-Year Follow-up Experience: The Framingham Study. *Annals of Internal Medicine* 1961; 55(1):33-50.

9. Jeffrey M. Hoeg, Evaluating Coronary Heart Disease Risk: Tiles in the Mosaic. *Journal of the American Medical Association* 1997; 277(17):1387-1390.
10. D. Hunninghake, LDL-Cholesterol as a Determinant of Coronary Heart Disease. *Clinical Therapeutics* 1990; 12(5):370-375.
11. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Journal of the American Medical Association* 1993; 269(23):3015-3023.
12. Robert L. Frye, Clinical Reality of Lowering Total and LDL Cholesterol. *Circulation* 1997; 95 (1):306-307.
13. Jacques E. Rossouw, Barry Lewis, and Basil M. Rifkind, The Value of Lowering Cholesterol After Myocardial Infarction. *New England Journal of Medicine* 1990; 323(16):1112-1119.
14. Patricia R. Hebert, et al., Cholesterol Lowering With Statin Drugs, Risk of Stroke, and Total Mortality. *Journal of the American Medical Association* 1997; 278(4):313-321.
15. H. Robert Superko, Beyond LDL Cholesterol Reduction. *Circulation* 1996; 94(10):2351-2354.
16. M. F. Oliver, Doubts About Preventing Coronary Heart Disease: Multiple Interventions in Middle Aged Men May Do More Harm Than Good. *British Medical Journal* 1992; 304:393-394.
17. M. F. Oliver, Might Treatment of Hypercholesterolaemia Increase Non-Cardiac Mortality? *Lancet* 1991; 337:1529-1531.
18. John C. LaRosa, Unresolved Issues in Early Trials of Cholesterol Lowering. *American Journal of Cardiology* 1995; 76:5C-9C.

19. Daniel Steinberg, Lewis A. Conner Memorial Lecture: Oxidative Modification of LDL and Atherogenesis. *Circulation* 1997; 95(4):1062-1071.
20. Mohammed H. Moghadasian, Bruce M. McManus, and Jiri J. Frohlich, Homocyst(e)ine and Coronary Artery Disease: Clinical Evidence and Genetic and Metabolic Background. *Archives of Internal Medicine* 1997; 157:2299-2308.
21. Robert S. Rosenson, Beyond Low-Density Lipoprotein Cholesterol: A Perspective on Low High-Density Lipoprotein Disorders and Lp(a) Lipoprotein Excess. *Archives of Internal Medicine* 1996; 156:1278-1284.
22. James H. Stein and Robert S. Rosenson, Lipoprotein Lp(a) Excess and Coronary Heart Disease. *Archives of Internal Medicine* 1997; 157:1170-1176.
23. David W. Bilheimer, Therapeutic Control of Hyperlipidemia in the Prevention of Coronary Atherosclerosis: A Review of Results from Recent Clinical Trials. *American Journal of Cardiology* 1988; 62:1J-9J.
24. D. Roger Illingworth, Lipid-Lowering Drugs: An Overview of Indications and Optimum Use. *Drugs* 1987; 33:259-279.
25. D. Roger Illingworth and Sandra Bacon, Hypolipidemic Effects of HMG-CoA Reductase Inhibitors in Patients with Hypercholesterolemia. *American Journal of Cardiology* 1987; 60:33G-42G.
26. Brian L. Strom, Chapter 24: How Should One Perform Pharmacoepidemiology Studies? Choosing Among the Available Alternatives. Pharmacoepidemiology, Second Edition. Brian L. Strom, ed., c1994:337-350.
27. Gary J. Okano, et al., Patterns of Antihypertensive Use Among Patients in the US Department of Defense Database Initially prescribed an ACE Inhibitor or Calcium Channel Blocker. *Clinical Therapeutics* 1997; 19(6):1433-1445.

28. Pharmacoeconomic Center, PEC Update. 16 October 1995; 96(01):1-A19.
29. Marshall E. Spearman, et al., Cost-Effectiveness of Initial Therapy with 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors to Treat Hypercholesterolemia in a Primary Care Setting of a Managed-Care Organization. *Clinical Therapeutics* 1997; 19(3):582-602.
30. American Heart Association. Atherosclerosis: A Major Cause of Cardiovascular Disease. <http://www.reg.uci.edu/UCI/CARDIOLOGY/PREVENTIVE/FACTS/athero.html>, January 1998.
31. Mohamad Navab, et al., Pathogenesis of Atherosclerosis. *American Journal of Cardiology* 1995; 76:18C-23C.
32. Andrew P. Selwyn, Scott Kinlay, and Peter Ganz, Atherogenesis and Ischemic Heart Disease. *American Journal of Cardiology* 1997; 80(8B):3H-7H.
33. A. L. Lehninger, D. L. Nelson, M. M. Cox, Chapter 20 - Lipid Biosynthesis. Principles of Biochemistry, Second Edition. Worth Publishers, New York, NY, c1993:674-682.
34. Consumers Report. The Cholesterol Question: What You Need to Know Now. *Consumers Reports* 1996; 61(3):36-37.
35. G. Steiner, Diabetes and Atherosclerosis: Metabolic Links. *Drugs* 1988; 36(Suppl. 3):22-26.
36. Mikko Syvanne and Marja-Riitta Taskinen, Lipids and Lipoproteins As Coronary Risk Factors in Non-Insulin-Dependent Diabetes Mellitus. *Lancet* 1997; 350(Supl. 1):20-23.
37. D. W. Bilheimer, The Lipoprotein Receptor Concept. *Drugs* 1988; 36(Suppl. 3):55-62.
38. D. Roger Illingworth, How Effective Is Drug Therapy in Heterozygous Familial Hypercholesterolemia? *American Journal of Cardiology* 1993; 72:54D-58D.

39. Pak-cheung Chan, et al., Surface Expression of Low Density Lipoprotein Receptor in EBV-Transformed Lymphocytes: Characterization and Use For Studying Familial Hypercholesterolemia. *Atherosclerosis* 1997; 131:149-160.
40. E. A. Stein, Drug and Alternative Therapies for Hyperlipidemia. *Atherosclerosis* 1994; 108(suppl.):S105-S116.
41. John A. Farmer and Antonio M. Gotto, Jr., Choosing the Right Lipid-Regulating Agent: A Guide to Selection. *Drugs* 1996; 52(5):649-661.
42. Mary McGrae McDermott, Brian Schmitt, and Elisabeth Wallner, Impact of Medication Nonadherence on Coronary Heart Disease Outcomes: A Critical Review. *Archives of Internal Medicine* 1997; 157:1921-1929.
43. Kathy Hitchens, Improving Cholesterol Compliance. *American Druggist* January 1996:34-37.
44. John Murphy and Gregor Coster, Issues in Patient Compliance. *Drugs* 1997; 54(6):797-800.
45. R. John Simes, on behalf of the PPP and CTT Investigators, Prospective Meta-Analysis of Cholesterol-Lowering Studies: The Prospective Pravastatin Pooling (PPP) Project and the Cholesterol Treatment Trialists (CTT) Collaboration. *American Journal of Cardiology* 1995; 76:122C-126C.
46. Vincent Maher, et al., Primary Prevention of Coronary Heart Disease: What Has WOSCOPS Told Us and What Questions Remain? *Drugs* 1997; 54(1):1-8.
47. James Shepherd, et al., Prevention of Coronary Heart Disease with Pravastatin in Men with Hypercholesterolemia. *New England Journal of Medicine* 1995; 333(20):1301-1307.
48. James Shepherd, for The West of Scotland Coronary Prevention Study Group, The West of Scotland Coronary Prevention Study: A Trial of

Cholesterol Reduction in Scottish Men. *American Journal of Cardiology* 1995; 76:113C-117C.

49. The West of Scotland Coronary Prevention Study Group, A Coronary Primary Prevention Study of Scottish Men Aged 45-64 Years: Trial Design. *Journal of Clinical Epidemiology* 1992; 45(8):849-860.
50. J. Caro, et al., The West of Scotland Coronary Prevention Study: Economic Benefit Analysis of Primary Prevention with Pravastatin. *British Medical Journal* 1997; 315(7122):1577-1582.
51. Andrew M. Tonkin, for the LIPID Study Group, Management of the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study after the Scandinavian Simvastatin Survival Study (4S). *American Journal of Cardiology* 1995; 76:107C-112C.
52. The Lipid Study Group, Design Features and Baseline Characteristics of the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) Study: A Randomized Trial in Patients with Previous Acute Myocardial Infarction and/or Unstable Angina Pectoris. *American Journal of Cardiology* 1995; 76:474-479.
53. John Kjekshus and Terje R. Pedersen, for the Scandinavian Simvastatin Survival Study Group, Reducing the Risk of Coronary Events: Evidence from the Scandinavian Simvastatin Survival Study (4S). *American Journal of Cardiology* 1995; 76:64C-68C.
54. Scandinavian Simvastatin Survival Study Group, Baseline Serum Cholesterol and Treatment Effect in the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1995; 345(8960):1274-1275.
55. Scandinavian Simvastatin Survival Study Group, Randomized Trial of Cholesterol Lowering in 4444 Patients with Coronary Heart Disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344(8934):1383-1389.
56. Terje R. Pedersen, et al., Safety and Tolerability of Cholesterol Lowering With Simvastatin During 5 Years in the Scandinavian Simvastatin Survival Study. *Archives of Internal Medicine* 1996; 156:2085-2092.

57. B. M. Rifkind, The Lipid Research Clinics Coronary Primary Prevention Trial. *Drugs* 1986; 31(Suppl. 1):53-60.
58. Benoit Lamarche, et al., Small, Dense Low-Density Lipoprotein Particles as a Predictor of the Risk of Ischemic Heart Disease in Men: Prospective Results From the Quebec Cardiovascular Study. *Circulation* 1997; 95(1):69-75.
59. Benoit Lamarche, et al., Apolipoprotein A-I and B Levels and the Risk of Ischemic Heart Disease During a Five-Year Follow-up of Men in the Quebec Cardiovascular Study. *Circulation* 1996; 94(3):273-278.
60. J. Stamler, et al., for the MRFIT Research Group. Relationship to Blood Pressure of Combinations of Dietary Macronutrients: Findings of the Multiple Risk Factor Intervention Trial (MRFIT). *Circulation* 1996; 94(10):2417-2423.
61. The Multiple Risk Factor Intervention Trial Research Group., Mortality After 16 Years for Participants Randomized to the Multiple Risk Factor Intervention Trial. *Circulation* 1996; 94(5):946-951.
62. J. Michael Gaziano, Patricia R. Hebert, and Charles H. Hennekens, Cholesterol Reduction: Weighing the Benefits and Risks. *Annals of Internal Medicine* 1996; 124(10):914-918.
63. P. H. Jones, Lovastatin and Simvastatin Prevention Studies. *American Journal of Cardiology* 1990; 66:39B-43B.
64. A. Lawrence Gould, et al., Cholesterol Reduction Yields Clinical Benefit: A New Look at Old Data. *Circulation* 1995; 91(8):2274-2282.
65. Ingar Holme, An Analysis of Randomized Trials Evaluating the Effect of Cholesterol Reduction on Total Mortality and Coronary Heart Disease Incidence. *Circulation* 1990; 82(6):1916-1924.
66. Matthew F. Muldoon, Stephen B. Manuck, and Karen A. Matthews, Lowering Cholesterol Concentrations and Mortality: A Quantitative

- Review of Primary Prevention Trials. *British Medical Journal* 1990; 301:309-314.
67. Robert M. Stark, Review of the Major Intervention Trials of Lowering Coronary Artery Disease Risk Through Cholesterol Reduction. *American Journal of Cardiology* 1996; 78(Suppl. 6A):13-19.
 68. Ingar Holme, Cholesterol Reduction and Its Impact on Coronary Artery Disease and Total Mortality. *American Journal of Cardiology* 1995; 76:10C-17C.
 69. Peter H. Jones and Antonio M. Gotto, Jr., Extending the Benefit of Lipid-Regulating Therapy to Primary Prevention. *American Journal of Cardiology* 1995; 76:118C-121C.
 70. Gilbert R. Thompson, What Targets Should Lipid-Modulating Therapy Achieve to Optimize the Prevention of Coronary Heart Disease? *Atherosclerosis* 1997; 131:1-5.
 71. Greg Brown, et al., Regression of Coronary Artery Disease as a Result of Intensive Lipid-Lowering Therapy in Men with High Levels of Apolipoprotein B. *New England Journal of Medicine* 1990; 323(19):1289-1298).
 72. B. Greg Brown, et al., Types of Change in Coronary Stenosis Severity and Their Relative Importance in Overall Progression and Regression of Coronary Disease. *Annals of the New York Academy of Science*
 73. David Waters, et al., Effects of Cigarette Smoking on the Angiographic Evolution of Coronary Atherosclerosis: A Canadian Coronary Atherosclerosis Intervention Trail (CCAIT) Substudy. *Circulation* 1996; 94:614-621.
 74. David Waters, et al., Effects of Monotherapy With an HMG-CoA Reductase Inhibitor on the Progression of Coronary Atherosclerosis as Assessed by Serial Quantitative Arteriography: The Canadian Coronary Atherosclerosis Intervention Trial. *Circulation* 1994; 89:959-968.

75. John Robert Crouse, et al., Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). *American Journal of Cardiology* 1995; 75:455-459.
76. Robert Patrick Byington, et al., Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). *American Journal of Cardiology* 1995; 76:54C-59C.
77. Jeffrey L. Probstfield, et al., for the ACAPS Research Group. Results of the Primary Outcome Measure and Clinical Events from the Asymptomatic Carotid Artery Progression Study. *American Journal of Cardiology* 1995; 75:47C-53C.
78. Riitta Salonen, et al., The Kuopio Atherosclerosis Prevention Study (KAPS): Effects of Pravastatin Treatment on Lipids, Oxidation Resistance of Lipoproteins, and Atherosclerotic Progression. *American Journal of Cardiology* 1995; 76:34C-39C.
79. Riitta Salonen, et al., Kuopio Atherosclerosis Prevention Study (KAPS): A Population-Based Primary Preventive Trial of the Effect of LDL Lowering on Atherosclerotic Progression in Carotid and Femoral Arteries. *Circulation* 1995; 92(7):1758-1764.
80. Eric de Groot, et al., Effect of Pravastatin on Progression and Regression of Coronary Atherosclerosis and Vessel Wall Changes in Carotid and Femoral Arteries: A Report from the Regression Growth Evaluation Statin Study. *American Journal of Cardiology* 1995; 76:40C-46C.
81. J. Wouter Jukema, et al., Effects of Lipid Lowering by Pravastatin on Progression and Regression of Coronary Artery Disease in Symptomatic Men With Normal to Moderately Elevated Serum Cholesterol Levels: The Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 1995; 91(10):2528-2540.
82. MAAS Investigators, Effect of Simvastatin on Coronary Atheroma: The Multicentre Anti-Atheroma Study (MAAS). *Lancet* 1994; 344(8923):633-638.

83. Frank M. Sacks, et al., for the Harvard Atherosclerosis Reversibility Project (HARP) Group, Effect on Coronary Atherosclerosis of Decrease in Plasma Cholesterol Concentrations in Normocholesterolaemic Patients. *Lancet* 1994; 344(8931):1182-1186.
84. Frank M. Sacks, et al., The Influence of Pretreatment Low Density Lipoprotein Cholesterol Concentrations on the Effect of Hypocholesterolemic Therapy on Coronary Atherosclerosis in Angiographic Trials. *American Journal of Cardiology* 1995; 76:78C-85C.
85. David H. Blankenhorn, et al., Coronary Angiographic Changes with Lovastatin Therapy: The Monitored Atherosclerosis Regression Study (MARS). *Annals of Internal Medicine* 1993; 119(10):969-976.
86. B. Greg Brown, et al., What Benefits Can Be Derived from Treating Normocholesterolemic Patients with Coronary Artery Disease. *American Journal of Cardiology* 1995; 76:93C-97C.
87. Jacques E. Rossouw, Lipid-Lowering Interventions in Angiographic Trials. *American Journal of Cardiology* 1995; 76:86C-92C.
88. Rakesh Sahni, et al., Prevention of Restenosis by Lovastatin After Successful Coronary Angioplasty. *American Heart Journal* 1991; 121(6, part 1):1600-1608.
89. William S. Weintraub, et al., Lack of Effect of Lovastatin on Restenosis After Coronary Angioplasty. *New England Journal of Medicine* 1994; 331(20):1331- 1337.
90. H. Iso, et al., for the MRFIT Research Group, Serum Cholesterol Levels and Six-Year Mortality From Stroke in 350,977 Men Screened for the Multiple Risk Factor Intervention Trial. *New England Journal of Medicine* 1989; 320(14):904-910.
91. SHEP Cooperative Research Group, Prevention of Stroke by Antihypertensive Drug Treatment in Older Persons With Isolated Systolic Hypertension: Final Results of the Systolic Hypertension in the Elderly Program (SHEP). *Journal of the American Medical Association* 1991; 265(24):3255-3264.

92. David Atkins, et al., Cholesterol Reduction and the Risk for Stroke in Men: A Meta-Analysis of Randomized, Controlled Trials. *Annals of Internal Medicine* 1993; 119(2):136-145.
93. Prospective Studies Collaboration, Cholesterol, Diastolic Blood Pressure, and Stroke: 13,000 Strokes in 450,000 People in 45 Prospective Cohorts. *Lancet* 1995; 346(8988):1647-1653.
94. Patricia R. Hebert, J. Michael Gaziano, and Charles H. Hennekens, An Overview of Trials of Cholesterol Lowering and Risk of Stroke. *Archives of Internal Medicine* 1995; 155(1):50-55.
95. D. Roger Illingworth and Jonathan A. Tobert, A Review of Clinical Trials Comparing HMG-CoA Reductase Inhibitors. *Clinical Therapeutics* 1994; 16(3):366-385.
96. Matti J. Tikkanen and Kalevi Pyorala, Cholesterol Reduction and Coronary Artery Disease: An Overview of Clinical Trials up to 1986. *Drugs* 1988; 36(Suppl. 3):27-31.
97. D. Roger Illingworth, An Overview of Lipid-Lowering Drugs. *Drugs* 1988; 36(Suppl. 3):63-71.
98. Helmut G. Schrott, et al., Adherence to National Cholesterol Education Program Treatment Goals in Postmenopausal Women With Heart Disease: The Heart and Estrogen/Progestin Replacement Study (HERS). *Journal of the American Medical Association* 1997; 277(16):1281-1286.
99. Marc A. Pfeffer, et al., Cholesterol and Recurrent Events: A Secondary Prevention Trial for Normolipidemic Patients. *American Journal of Cardiology* 1995;76:98C-106C.
100. L. Tenkanen, M. Manttari, and V. Manninen, Some Coronary Risk Factors Related to the Insulin Resistance Syndrome and Treatment With Gemfibrozil. *Circulation* 1995; 92:1779-1785.
101. Jussi K. Huttunen, et al., Helsinki Heart Study: New Perspectives in the Prevention of Coronary Heart Disease. *Drugs* 1988; 36(Suppl. 3):32-36.

102. Charles L. Shear, et al., Expanded Clinical Evaluation of Lovastatin (EXCEL) Study Results: Effect of Patient Characteristics on Lovastatin-Induced Changes in Plasma Concentrations of Lipids and Lipoproteins. *Circulation* 1992; 85:1293-1303.
103. Reagan H. Bradford, et al., Expanded Clinical Evaluation of Lovastatin (EXCEL) Study Results: I. Efficacy in Modifying Plasma Lipoproteins and Adverse Event Profile in 8245 Patients With Moderate Hypercholesterolemia. *Archives of Internal Medicine* 1991; 151:43-49.
104. Reagan H. Bradford, et al., Expanded Clinical Evaluation of Lovastatin (EXCEL) Study: Design and Patient Characteristics of a Double-Blind, Placebo-Controlled Study in Patients with Moderate Hypercholesterolemia. *American Journal of Cardiology* 1990; 66:44B-55B.
105. Philip H. Frost, et al., Coronary Heart Disease Risk Factors in Men and Women Aged 60 Years and Older: Findings From the Systolic Hypertension in the Elderly Program. *Circulation* 1996; 94(1):26-34.
106. Philip H. Frost, et al., Serum Lipids and Incidence of Coronary Heart Disease: Findings From the Systolic Hypertension in the Elderly Program (SHEP). *Circulation* 1996; 94(10):2381-2388.
107. Annelies W. E. Weverling-Rijnsburger, et al., Total Cholesterol and Risk of Mortality in the Oldest Old. *Lancet* 1997; 350(9085):1119-1123.
108. Assiamira Ferrara, Elizabeth Barrett-Connor, and Jun Shan, Total, LDL, and HDL Cholesterol Decrease With Age in Older Men and Women: The Rancho Bernardo Study 1984-1994. *Circulation*. 1997; 96(1):37-43.
109. Weihang Bao, et al., Usefulness of Childhood Low-Density Lipoprotein Cholesterol Level in Predicting Adult Dyslipidemia and Other Cardiovascular Risks: The Bogalusa Heart Study. *Archives of Internal Medicine* 1996; 156:1315-1320.
110. Weihang Bao, et al., Longitudinal Changes in Cardiovascular Risk From Childhood to Young Adulthood in Offspring of Parents With Coronary

Artery Disease: The Bogalusa Heart Study. *Journal of the American Medical Association* 1997; 278(21):1749-1754.

111. Braxton D. Mitchell, et al., Genetic and Environmental Contributions to Cardiovascular Risk Factors in Mexican Americans: The San Antonio Family Heart Study. *Circulation* 1996; 94(9):2159-2170.
112. M. Ilyas Kamboh, et al., Plasma Apolipoprotein A-I, Apolipoprotein B, and Lipoprotein(a) Concentrations in Normoglycemic Hispanics and Non-Hispanic Whites from the San Luis Valley, Colorado. *American Journal of Epidemiology* 1997; 146(12):1011-1018.
113. Richard F. Gillum, Michael E. Mussolino, and Jennifer H. Madans, Coronary Heart Disease Incidence and Survival in African-American Women and Men: The NHANES I Epidemiologic Follow-up Study. *Annals of Internal Medicine* 1997; 127(2):111-118.
114. Andrew P. Lea and Donna McTavish, Atorvastatin: A Review of its Pharmacology and Therapeutic Potential in the Management of Hyperlipidaemias. *Drugs* 1997; 53(5):828-847.
115. Marieke Dekker Schoen, Lipid Management: An Opportunity for Pharmacy Service. *Journal of the American Pharmaceutical Association* 1996; NS36(10):609-619.
116. John W. Grunden and Kenneth A. Fisher, Lovastatin-Induced Rhabdomyolysis Possibly Associated with Clarithromycin and Azithromycin. *Annals of Pharmacotherapy* 1997; 31(7-8):859-863.
117. Lisa S. McCormick, et al., Rationale, Design, and Baseline Characteristics of a Trial Comparing Aggressive Lipid Lowering with Atorvastatin Versus Revascularization Treatments (AVERT). *American Journal of Cardiology* 1997; 80:1130-1133.
118. M. H. Davidson, et al., Effectiveness of Atorvastatin for Reducing Low-Density Lipoprotein Cholesterol to National Cholesterol Education Program Treatment Goals. *American Journal of Cardiology* 1997; 80(3):347-348.

119. Therese M. Heinonen, et al., The Lipid-Lowering Effects of Atorvastatin, a New HMG-CoA Reductase Inhibitor: Results of a Randomized, Double-Masked Study. *Clinical Therapeutics* 1996; 18(5):853-863.
120. W. Leonhardt, et al., Effects of Fluvastatin Therapy on Lipids, Antioxidants, Oxidation of Low Density Lipoproteins and Trace Metals. *European Journal of Clinical Pharmacology* 1997; 53(1):65-69.
121. Osamah Hussein, et al., Reduced Susceptibility of Low Density Lipoprotein (LDL) to Lipid Peroxidation After Fluvastatin Therapy is Associate with the Hypcholesterolemic Effect of the Drug and its Binding to the LDL. *Atherosclerosis* 1997; 128:11-18.
122. J. Alan Herd, et al., Effects of Fluvastatin on Coronary Atherosclerosis in Patients With Mild to Moderate Cholesterol Elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). *American Journal of Cardiology* 1997; 80:278-286.
123. H. Robert Superko, R. M. Krauss. and C. DiRicco, Effect of Fluvastatin on Low-Density Lipoprotein Peak Particle Diameter. *American Journal of Cardiology* 1997; 80:78-81.
124. Robert H. Knopp and Jiri J. Frolich, Efficacy and Safety of Fluvastatin in Patients with Non-Insulin-Dependent Diabetes Mellitus and Hyperlipidemia: Preliminary Report. *American Journal of Cardiology* 1994; 73:39D-41D.
125. J. Alan Herd, et al., Baseline Characteristics of Subjects in the Lipoprotein and Coronary Atherosclerosis Study (LCAS) with Fluvastatin. *American Journal of Cardiology* 1994; 73:42D-49D.
126. David P. Foley, et al., on behalf of the FLARE study group, Prevention of Restenosis After Coronary Balloon Angioplasty: Rationale and Design of the Fluvastatin Angioplasty Restenosis (FLARE) Trial. *American Journal of Cardiology* 1994; 73:50D-61D.

127. Eran Leitersdorf, Gender-Related Response to Fluvastatin in Patients with Heterozygous Familial Hypercholesterolaemia. *Drugs* 1994; 47(Suppl. 2):54-63.
128. T. K. Peters, E. N. Muratti, and M. Mehra, Efficacy and Safety of Fluvastatin in Women with Primary Hypercholesterolaemia. *Drugs* 1994; 47(Suppl. 2):64-72.
129. John R. Downs, et al., Design & Rationale of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *American Journal of Cardiology* 1997; 80:287-293.
130. Vincent C. Dennis, et al., The Use of Alternate-Day Lovastatin in Hypercholesterolemic Men. *Annals of Pharmacotherapy*. 1997; 31:708-712.
131. Thomas C. Andrews, et al., Effect of Cholesterol Reduction on Myocardial Ischemia in Patients With Coronary Disease. *Circulation* 1997; 95(2):324-328.
132. Curt D. Furberg, et al., for the Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group, Effect of Lovastatin on Early Carotid Atherosclerosis and Cardiovascular Events. *Circulation* 1994; 90(4):1679-1687.
133. William B. Kannel, et al., Efficacy and Tolerability of Lovastatin in a Six-Month Study: Analysis by Gender, Age and Hypertensive Status. *American Journal of Cardiology* 1990; 66:1B-10B.
134. Geraldine Mantell, Theresa Burke and Joan Staggers, Extended Clinical Safety Profile of Lovastatin. *American Journal of Cardiology* 1990; 66:11B-15B.
135. Abhimanyu Garg and Scott M. Grundy, Treatment of Dyslipidemia in Non-Insulin-Dependent Diabetes Mellitus with Lovastatin. *American Journal of Cardiology* 1988; 62:44J-49J.
136. Y. Narita, et al., Increase or Decrease of HDL-Cholesterol Concentrations During Pravastatin Treatment Depending on the Pre-Treatment HDL

Cholesterol Levels. *European Journal of Clinical Pharmacology* 1997; 52(6):461-463.

137. Jun Muramatsu, et al., Hemodynamic Changes Associated with Reduction in Total Cholesterol by Treatment with the HMG-CoA Reductase Inhibitor Pravastatin. *Atherosclerosis* 1997; 130:179-182.
138. Frank M. Sacks, et al., The Effect of Pravastatin on Coronary Events after Myocardial Infarction in Patients with Average Cholesterol Levels. *New England Journal of Medicine* 1996; 335(14):1001-1009.
139. Curt D. Furberg, et al., for the PLAC I and PLAC II Investigators, Reduction in Coronary Events During Treatment with Pravastatin. *American Journal of Cardiology* 1995; 76:60C-63C.
140. Shigeto Morimoto, et al., Long-Term Effects of Pravastatin on Serum Lipid Levels in Elderly Patients with Hypercholesterolemia. *Clinical Therapeutics* 1994; 16(5):793-803.
141. Curt D. Furberg, et al., Pravastatin, Lipids, and Major Coronary Events. *American Journal of Cardiology* 1994; 73:1133-1134.
142. The Pravastatin Multinational Study Group for Cardiac Risk Patients, Effects of Pravastatin in Patients with Serum Total Cholesterol Levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) Plus Two Additional Atherosclerotic Risk Factors. *American Journal of Cardiology* 1993; 72:1031-1037.
143. H. Honjo, et al., Menopause and Hyperlipidemia: Pravastatin Lowers Lipid Levels Without Decreasing Endogenous Estrogens. *Clinical Therapeutics* 1992; 14(5):699-707.
144. Henry Y. Pan, et al., Comparative Efficacy of Once-Daily Versus Twice-Daily Pravastatin in Primary Hypercholesterolemia. *Clinical Therapeutics* 1991; 13(3):368-372.
145. Frederick J. Raal, et al., Statin Therapy in a Kindred with Both Apolipoprotein B and Low Density Lipoprotein Receptor Gene Defects. *Atherosclerosis* 1997; 129:97-102.

146. S. Vitols, B. Angelin and G. Juliusson, Simvastatin Impairs Mitogen-Induced Proliferation of Malignant B-Lymphocytes from Humans - In Vitro and In Vivo Studies. *Lipids* 1997; 32(3):255-262.
147. Gerard O'Driscoll, Danny Green, and Roger Taylor, Simvastatin, and HMG-Coenzyme A Reductase Inhibitor, Improves Endothelial Function Within 1 Month. *Circulation* 1997; 95(5):1126-1131.
148. Magnus Johannesson, et al., for the Scandinavian Simvastatin Survival Study Group, Cost Effectiveness of Simvastatin Treatment to Lower Cholesterol Levels in Patients with Coronary Heart Disease. *New England Journal of Medicine* 1997; 336(5):332-336.
149. Hiroshi Yoshida, et al., Effects of Low-Dose Simvastatin on Cholesterol Levels, Oxidative Susceptibility, and Antioxidant Levels of Low-Density Lipoproteins on Patients with Hypercholesterolemia: A Pilot Study. *Clinical Therapeutics* 1995; 17(3):379-389.
150. Hajime Ide, et al., Effects of Simvastatin, an HMG-CoA Reductase inhibitor, on Plasma Lipids and Steroid Hormones. *Clinical Therapeutic* 1990; 12(5):410-420.
151. Roberto Antonicelli, et al., Simvastatin in the Treatment of Hypercholesterolemia in Elderly Patients. *Clinical Therapeutics* 1990; 12(2):165-171.
152. Keifiro Saku, Jun Sasaki, and Kikuo Arakawa, Low-Dose Effect of Simvastatin (MK-733) on Serum Lipids, Lipoproteins, and Apolipoproteins in Patients with Hypercholesterolemia. *Clinical Therapeutics* 1989; 11(2):247-257.
153. Terry A. Jacobson and Louis F. Amorosa, Combination Therapy with Fluvastatin and Niacin in Hypercholesterolemia: A Preliminary Report on Safety. *American Journal of Cardiology* 1994; 73:25D-29D.
154. Eleonora Muratti, Tim K. Peters, and Eran Leitersdorf, Fluvastatin in Familial Hypercholesterolemia: A Cohort Analysis of the Response to

Combination Treatment. *American Journal of Cardiology* 1994; 73:30D-38D.

155. B. Greg Brown, et al., Moderate Dose, Three-Drug Therapy With Niacin, Lovastatin, and Colestipol to Reduce Low-Density Lipoprotein Cholesterol <100 mg/dl in Patients With Hyperlipidemia and Coronary Artery Disease. *American Journal of Cardiology* 1997; 80:111-115.
156. Todd J. Anderson, et al., The Effect of Cholesterol-Lowering and Antioxidant Therapy on Endothelium-Dependent Coronary Vasomotion. *New England Journal of Medicine* 1995; 332(8):488-493.
157. Daniel Yeshurun, et al., Treatment of Severe, Resistant Familial Combined Hyperlipidemia with a Bezafibrate-Lovastatin Combination. *Clinical Therapeutics* 1993; 15(2):355-363.
158. Stephenae F. Gardner, et al., Combination of Low-Dose Niacin and Pravastatin Improves the Lipid Profile in Diabetic Patients Without Compromising Glycemic Control. *Annals of Pharmacotherapy* 1997; 31:677-682.
159. Klaus U. Kirchgassler, Julia Schiffner-Rohe, and Ursula Stahlheber, Cost Effectiveness of Micronised Fenofibrate and Simvastatin in the Short Term Treatment of Type IIa and Type IIb Hyperlipidemia. *Pharmacoeconomics* 1997; 12(2 Pt 2):237-246.
160. Jose L. Zambrana, et al., Comparison of Bezafibrate Versus Lovastatin for Lowering Plasma Insulin, Fibrinogen, and Plasminogen Activator Inhibitor-1 Concentrations in Hyperlipemic Heart Transplant Patients. *American Journal of Cardiology* 1997; 80:836-840.
161. David S. H. Bell, A Comparison of Lovastatin, an HMG-CoA Reductase Inhibitor, with Gemfibrozil, a Fibrinic Acid Derivative, In the Treatment of Patients with Diabetic Dyslipidemia. *Clinical Therapeutics* 1995; 17(5):901-910.
162. Ronald Goldberg, et al., Comparison of the Effects of Lovastatin and Gemfibrozil on Lipids and Glucose Control in Non-Insulin-Dependent Diabetes Mellitus. *American Journal of Cardiology* 1990; 66:16B-21B.

163. The Lovastatin Study Group IV, A Multicenter Comparison of Lovastatin and Probucol for Treatment of Severe Primary Hypercholesterolemia. *American Journal of Cardiology* 1990; 66:22B-30B.
164. Matti J. Tikkanen, et al., Comparison Between Lovastatin and Gemfibrozil in the Treatment of Primary Hypercholesterolemia: The Finnish Multicenter Study. *American Journal of Cardiology* 1988;62:35J-43J.
165. Michael H. Davidson, et al., A Comparison of Estrogen Replacement, Pravastatin, and Combined Treatment for the Management of Hypercholesterolemia in Postmenopausal Women. *Archives of Internal Medicine* 1997; 157(11):1186-1192.
166. Amos Pines, Yoran Levo, and Daniel Ayalon, Hormone-Replacement Therapy Compared with Simvastatin for Postmenopausal Women with Hypercholesterolemia. *New England Journal of Medicine* 1998; 338(1):63-64.
167. Giselle M. Darling, et al., Estrogen and Progestin Compared with Simvastatin for Hypercholesterolemia in Postmenopausal Women. *New England Journal Medicine* 1997; 337(9):595-601.
168. Paul Nestel, et al., A Comparative Study of the Efficacy of Simvastatin and Gemfibrozil in Combined Hyperlipoproteinemia: Prediction of Response by Baseline Lipids, Apo E Genotype, Lipoprotein(a) and Insulin. *Atherosclerosis* 1997; 129:231-239.
169. Anna E. Sweaney, et al., Effects of Simvastatin Versus Gemfibrozil on Lipids and Glucose Control in Patients with Non-Insulin-Dependent Diabetes Mellitus. *Clinical Therapeutics* 1995; 17(2):186-203.
170. Stefano Bertolini, et al., Efficacy and safety of Atorvastatin Compared to Pravastatin in Patients with Hypercholesterolemia. *Atherosclerosis* 1997; 130:191-197.

171. Rossitea Naoumova, et al., Prolonged Inhibition of Cholesterol Synthesis Explains the Efficacy of Atorvastatin. *Journal of Lipid Research* 1997; 38(7):1496-1500.
172. Anthony Dart, et al., A Multicenter, Double-Blind, One-Year Study Comparing Safety and Efficacy of Atorvastatin Versus Simvastatin in Patients with Hypercholesterolemia. *American Journal of Cardiology* 1997; 80:39-44.
173. Donald Black, et al., Cost Effectiveness of Treatment to National Cholesterol Education Panel (NCEP) Targets with HMG-CoA Reductase Inhibitors: Trial Design. *Pharmacoeconomics* 1997; 12 (2 Pt 2):278-285.
174. Joseph P. Rindone, et al., Changes in Serum Lipids When Fluvastatin is Substituted for Lovastatin in the Same Doses. *American Journal of Cardiology* 1997; 80(3):348-349.
175. David T. Nash, Meeting National Cholesterol Education Goals in Clinical Practice - A Comparison of Lovastatin and Fluvastatin in Primary Prevention. *American Journal of Cardiology* 1996; 78(suppl 6A):26-31.
176. Lisa Korman and Lydia Borysiuk, Replacing Lovastatin with Pravastatin: Effect on Serum Lipids and Costs. *American Journal of Health-System Pharmacy* 1995; 52(10):1078-1082.
177. John A. Farmer, et al., Comparative Effects of Simvastatin and Lovastatin in Patients with Hypercholesterolemia. *Clinical Therapeutics* 1992; 14(5):708-717.
178. Ruth McPherson, Comparison of the Short-Term Efficacy and Tolerability of Lovastatin and Pravastatin in the Management of Primary Hypercholesterolemia. *Clinical Therapeutics* 1992; 14(2):276-291.
179. Pier L. Malini, et al., Simvastatin Versus Pravastatin: Efficacy and Tolerability in Patients with Primary Hypercholesterolemia. *Clinical Therapeutics* 1991; 13(4):500-509.

180. Rebecca G. Bakker-Arkema, et al., A Brief Review Paper of the Efficacy and Safety of Atorvastatin in Early Clinical Trials. *Atherosclerosis* 1997; 131:17-23.
181. William R. Garnett, A Review of Current Clinical Findings with Fluvastatin. *American Journal of Cardiology* 1996; 78(suppl 6A):20-25.
182. Jean-Paul Deslypere, Clinical Implications of the Biopharmaceutical Properties of Fluvastatin. *American Journal of Cardiology* 1994; 73:12D-17D.
183. Leonard A. Jokubaitis, Updated Clinical Safety Experience with Fluvastatin. *American Journal of Cardiology* 1994; 73:18D-24D.
184. Alfred W. Alberts, Discovery, Biochemistry and Biology of Lovastatin. *American Journal of Cardiology* 1988; 62:10J-15J.
185. Jonathan A. Tobert, Efficacy and Long-Term Adverse Effect Pattern of Lovastatin. *American Journal of Cardiology* 1988; 62:28J-34J.
186. D. Roger Illingworth, Therapeutic Use of Lovastatin in the Treatment of Hypercholesterolemia. *Clinical Therapeutics* 1994; 16(1):2-26.
187. Robert P. Byington, et al., Reduction in Cardiovascular Events During Pravastatin Therapy: Pooled Analysis of Clinical Events of the Pravastatin Atherosclerosis Intervention Program. *Circulation* 1995; 92(9):2419-2425.
188. Sheldon X. Kong, et al., Efficacy of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors in the Treatment of Patients with Hypercholesterolemia: A Meta-Analysis of Clinical Trials. *Clinical Therapeutics* 1997; 19(4):778-797.
189. Peter H. Jones, Lovastatin and Simvastatin Prevention Studies. *American Journal of Cardiology* 1990; 66:39B-43B.
190. Sidney C. Smith, Review of Recent Clinical Trials of Lipid Lowering in Coronary Artery Disease. *American Journal of Cardiology* 1997; 80(8B):10H-13H.

191. Thomas B. Newman and Stephen B. Hulley, Carcinogenicity of Lipid-Lowering Drugs. *Journal of the American Medical Association* 1996; 275(1):55-60.
192. James E. Dalen and William S. Dalton, Commentary: Does Lowering Cholesterol Cause Cancer? *Journal of the American Medical Association* 1996; 275(1):67-69.
193. Terry A. Jacobson, Cost-Effectiveness of 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitor Therapy in the Managed Care Era. *American Journal of Cardiology* 1996; 78(Suppl. 6A):32-41.
194. Zafar Hakim, Jerome Pierson, and Deva S. Pathak, A Proposed Model for Conducting Institutional-Specific Cost-Effectiveness Analysis: A Case Study of Lipid-Lowering Agents. *Pharmacy Practice and Management Quarterly* 1996; 16(1):79-97.
195. Leon L. Martens and Remi Guilbert, Cost-Effectiveness Analysis of Lipid-Modifying Therapy in Canada: Comparison of HMG-CoA Reductase Inhibitors in the Primary Prevention of Coronary Heart Disease. *Clinical Therapeutics* 1994; 16(6):1052-1062.
196. George D. Smith and Juha Pekkanen, For Debate: Should There Be a Moratorium on the Use of Cholesterol Lowering Drugs? *British Medical Journal* 1992; 304:431-434.
197. Conrad B. Blum, Comparison of Properties of Four Inhibitors of 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase. *American Journal of Cardiology* 1994; 73:3D-11D.
198. Scott M. Grundy, Gloria L. Vega, and Abhimanyu Garg, Use of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors in Various Forms of Dyslipidemia. *American Journal of Cardiology* 1990; 66:31B-38B.
199. Patricia R. Hebert, et al., Cholesterol Lowering With Statin Drugs, Risk of Stroke, and Total Mortality. *Journal of the American Medical Association* 1997; 278(4):313-321.

200. Scott M. Grundy, HMG-CoA Reductase Inhibitors for Treatment of Hypercholesterolemia. *New England Journal of Medicine* 1988; 319(1):24-33.
201. Eve E. Slater and James S. MacDonald, Mechanism of Action and Biological Profile of HMG CoA Reductase Inhibitors: A New Therapeutic Alternative. *Drugs* 1988; 36(Suppl. 3):72-82.
202. D. Roger Illingsworth, Therapeutic Use of Lovastatin in the Treatment of Hypercholesterolemia. *Clinical Therapeutics* 1994; 16(1):2-26.
203. Malini Haria and Donna McTavish, Pravastatin: A Reappraisal of its Pharmacological Properties and Clinical Effectiveness in the Management of Coronary Heart Disease. *Drugs* 1997; 53(2):299-336.
204. Harri Niinikoski, et al., Prospective Randomized Trial of Low-Saturated-Fat, Low-Cholesterol Diet During the First 3 Years of Life: The STRIP Baby Project. *Circulation* 1996; 94:1386-1393.
205. Darwin R. Labarthe, et al., Development of Cardiovascular Risk Factors From Ages 8 to 18 in Project HeartBeat!: Study Design and Patterns in Plasma Total Cholesterol Concentration. *Circulation* 1997; 95:2636-2642.
206. Kimmo V. K. Porkka, et al., Trends in Serum Lipid Levels during 1980-1992 in Children and Young Adults: The Cardiovascular Risk in Young Finns Study. *American Journal of Epidemiology* 1997; 146(1):64-77.
207. William B. Kannel, Range of Serum Cholesterol Values in the Population Developing Coronary Artery Disease. *American Journal of Cardiology* 1995; 76:69C-77C.
208. Alan O. Marcus, Rationale for Effective Treatment of Hypercholesterolemia. *American Journal of Cardiology* 1996; 78(suppl 6A):4-12.
209. Clifford L. Johnson, et al., Declining Serum Total Cholesterol Levels Among US Adults: The National Health and Nutrition Examination

Surveys. *Journal of the American Medical Association* 1993; 269(23):3002-3008.

210. Christopher T. Sempos, et al., Prevalence of High Blood Cholesterol Among US Adults: An Update Based on Guidelines From the Second Report of the National Cholesterol Education Program Adult Treatment Panel. *Journal of the American Medical Association* 1993; 269(23):3009-3014.
211. Carlos Iribarren, et al., Twelve-Year Trends in Cardiovascular Disease Risk Factors in the Minnesota Heart Survey: Are Socioeconomic Differences Widening? *Archives of Internal Medicine* 1997; 157(8):873-881.
212. Edgar R. Gonzalez, Preventing Cardiovascular Atherosclerosis: Role of HMG-CoA Reductase Inhibitors. *Formulary* 1996; 31(7):582-602.
213. Gregory R. Wise and Trang T. Schultz, Hyperlipidemia: When Does Treatment Make a Difference? *Post Graduate Medicine* 1996; 100(1):138-149.
214. P. Plans Rubio, Cost-Effectiveness of Dietary Treatment of Hypercholesterolemia in Spain. *Public Health* 1997; 111(1):33-40.
215. James P. McCormick, Marc Levine, and Robert E. Rango, Primary Prevention of Heart Disease and Stroke: A Simplified approach to Estimating Risk of Events and Making Drug Treatment Decisions. *Canadian Medical Association Journal* 1997; 157(4):422-428.
216. V. F. Carr and J. C. Walker, Formulary Management in a Military Treatment Facility. *Military Medicine* 1997; 162(3):205-208.
217. Chuck Appleby, The Mouse That Roared. *Hospitals & Health Networks*. 1996; 70(4):31-36.
218. Wendy Herr, Data Integration: HFMA Study Findings. *Healthcare Financial Management* September 1996:52-56.

219. Brian L. Strom, Chapter 23: Other Approaches to Pharmacoepidemiology Studies. Pharmacoepidemiology, Second edition. Brian L. Strom, ed., c1994:323-335.
220. W. Robert Simons and M. Eugene Smith, Health Economics and Outcomes Research with Retrospective Data. *Clinical Therapeutics* 1994; 16(6):1063-1067.
221. Brenda R. Motheral and Kathleen A. Fairman, The Use of Claims Databases for Outcomes Research: Rationale, Challenges, and Strategies. *Clinical Therapeutics* 1997; 19(2):346-366.
222. Clement J. McDonald, et al., A Framework for Capturing Clinical Data Sets from Computerized Sources. *Annals of Internal Medicine* 1997; 127(8 Pt 2):675-682.
223. Lawrence Gostin, Health Care Information and the Protection of Personal Privacy: Ethical and Legal Considerations. *Annals of Internal Medicine* 1997; 127 (8 Pt 2):683-690.

CHAPTER TWO

METHODOLOGY

This chapter presents a discussion of the design of the study. Included are: (1) the source of the data; (2) a brief description of the study population and the criteria used in the selection of the final study subjects; (3) a brief description of the study design; (4) the how, what, and why of data collection for the study; and (5) how the data were analyzed for each of the three objectives.

DATA SOURCE

The Department of Defense's (DoD) Composite Health Care System (CHCS) computer system in the greater San Antonio, Texas, area was the primary data source. The aggregate prescription database maintained by DoD Pharmacoeconomic Center (PEC) personnel was used as a supplemental data source.

STUDY POPULATION

Military beneficiaries receiving HMG-CoA reductase inhibitor (statin) prescriptions between 28 Feb. 96 and 4 Apr. 98 at any of the five Military Treatment Facilities (MTFs) in the greater San Antonio area using the CHCS system were eligible for this study. The study selection criteria included being statin-naïve (a minimum of six months of "statin-free" prescription history prior

to the initial statin prescription), having at least two low-density lipoprotein (LDL) levels on record (one before statin therapy and one after initiation of statin therapy), and having received more than a single prescription fill for a statin drug.

Potential subjects were identified by running a drug utilization review (DUR) report for new statin patients during three selected months, October, 1996, April, 1997, and October, 1997. As patients identified to be potential subjects were followed backward in time to the initial statin prescription fill, this researcher felt these three months, although not randomly selected, would allow sufficient diversity for capture of statin naive patients.

The target population was narrowed to statin-naive individuals so that more accurate pre- and post-statin LDL levels could be determined. The 1990 Food and Drug Administration (FDA) guideline on clinical evaluation of anti-hyperlipidemia therapy¹ recommends that three pre-treatment labs be performed, with draw intervals of one to four weeks being optimal. The laboratories at the MTFs in the greater San Antonio area use the Friedewald formula to calculate LDL levels. This is done by calculating LDL from total cholesterol (TC), high-density lipoprotein (HDL), triglycerides (TG), and/or very-low-density lipoprotein (VLDL) as shown below:

$$\text{LDL} = \text{TC} - \text{HDL} - (\text{TG}/5) \quad \text{or}$$
$$\text{LDL} = \text{TC} - \text{HDL} - \text{VLDL}$$

This equation is invalid when TG is 400 mg/dl or higher, with the LDL value being reported as zero or missing.² A minimum of two recorded non-zero low

density lipoprotein (LDL) cholesterol blood levels, one before statin therapy and one after initiation of statin therapy was used for the purposes of this study.

Although the literature establishes a minimum of 80 percent compliance³, this is an actual-use study, so all compliance rates were allowed. Compliance was calculated by adding up all the medication the patient received from the first statin prescription to the last statin fill (excluding the amount of medication received in the final fill), expressed in number of days supply (one tablet twice a day, #180, was recorded as a 90-day supply), dividing this by the number of days between the initial statin prescription and the last recorded statin fill, rounded to months (for example, 1 Apr. 96 to 31 Mar. 98 was counted as 690 days just as 31 Apr. 96 to 1 Mar. 98), and then multiplied by 100 to give the percent compliance. Patients who received only a single filling of a statin prescription were not included in the study. It was assumed that all medication had been taken by the patient when the prescription was refilled.

Patient therapy and target LDL levels are based on stratification of patients into primary or secondary prevention and then subdivided further based on presence of negative or positive risk factors. Patients were categorized into primary (without established coronary heart disease) or secondary (with established coronary heart disease) prevention based on drug therapy received. Upon the advice of Dr. Robert Talbert, Professor at the University of Texas, a very conservative approach of nitrate use or admission to a coronary care unit (CCU) was used to classify patients as secondary prevention (those with established coronary heart disease (CHD)) or primary prevention (those without established CHD).⁴ Subjects were stratified by risk factor and comorbid

conditions, using specific drug therapy as a surrogate for the more routinely used diagnoses codes (with guidance from Dr. Talbert). Table 2.1 lists the risk factors other than LDL for CHD, showing that positive risk factors (at risk for developing CHD) include being a male over 45 years of age, a female over 55 years of age or under that age with premature menopause and no oral estrogen replacement therapy, having a family history of premature CHD, having a history of cigarette smoking, having hypertension, having a low HDL level (< 35 mg/dl or 0.9 mmol/L), or having diabetes mellitus. Table 2.1 also shows that having a high HDL level (≥ 60 mg/dl or 1.6 mmol/L) is a negative risk factor (it has been associated with decreased risk of developing CHD).

Table 2.1 CHD Risk Factors Other Than LDL

POSITIVE RISK FACTORS	NEGATIVE RISK FACTORS
<ul style="list-style-type: none"> - Age <ul style="list-style-type: none"> Male ≥ 45 years of age Female ≥ 55 years of age or premature menopause without oral estrogen replacement therapy - Family history of premature CHD - Cigarette smoking - Hypertension - Low HDL level (≤ 35 mg/dl) - Diabetes mellitus 	<ul style="list-style-type: none"> - High HDL level (≥ 60 mg/dl)

Table 2.2 shows the target LDL levels post-treatment, as stratified by risk category, and is based on the National Cholesterol Education Program (NCEP) Guidelines.⁵ Those with established CHD should achieve an LDL level of ≤ 100 mg/dl (or 2.6 mmol/L). Those without established CHD, but with two or more risk factors, should achieve an LDL level of < 130 mg/dl (or 3.4 mmol/L). Those without established CHD and with less than two risk factors should achieve an LDL level of < 160 mg/dl (or 4.1 mmol/L).

Table 2.2 Treatment Goals, Based on NCEP Guidelines

Patient Stratification by Risk Category	LDL Level for Initiation of Drug Therapy	LDL Goal of Therapy
Secondary Prevention - With CHD	≥ 130 mg/dl	≤ 100 mg/dl
Primary Prevention - Without CHD - With ≥ 2 risk factors (High Risk)	≥ 160 mg/dl	< 130 mg/dl
Primary Prevention - Without CHD - With < 2 risk factors (Low Risk)	≥ 190 mg/dl	< 160 mg/dl

STUDY DESIGN

This was a longitudinal retrospective analysis of an existing database in the non-randomized, multiple group, pretest-posttest format. As shown below, the observations (**O**) to the left of the intervention (initiation of statin therapy or **X**) represent the pre-therapy mean LDL levels while the observations to the right of the intervention represent the post-therapy LDL levels, which will be calculated as both the mean overall post-treatment LDL value and the difference between the mean pre-treatment and final LDL value.

O₁	X₁	O₂	Atorvastatin
O₃	X₂	O₄	Fluvastatin
O₅	X₃	O₆	Lovastatin
O₇	X₄	O₈	Pravastatin
O₉	X₅	O₁₀	Simvastatin

DATA COLLECTION

Data collection was performed solely by this researcher. Data were collected from CHCS at a computer terminal at the PEC or by remote modem access from the researcher's home in San Antonio. Only the researcher had access to the complete patient information files and a unique identification number was assigned to each subject once all data were collected (patient names and social security numbers were removed for patient privacy).

To determine if the patient met the selection criteria previously described, different portions of the CHCS computer system were utilized. CHCS does not have a fully integrated database, so structured queries combining information from different disciplines (patient records, pharmacy, and lab) were impractical.

Therefore, the information residing in each area was gathered by manually looking up each patient in that particular portion of CHCS, transcribing the data onto printed-out worksheets, and then entering the coded data into a Statistical Processing for the Social Sciences (SPSS) data file.

Patient demographic information was gathered from the patient registration records field and included patient age, sex, branch of service/member type (such as active duty Air Force member vs. Navy retired family member), race/ethnicity, whether the patient had any other medical insurance (those 65 years of age or older were assumed to have Medicare insurance), and whether a Texas or out-of-state address was on file for the patient. Other than the assumption concerning Medicare insurance in those over 65 years of age, if the information was missing, it was coded as such ("."). The data were either entered numerically (such as patient age) or categorically (such as sex, service type, race, insurance, and address).

The prescription portion of CHCS was examined to determine prior statin usage, prescription fill/refill history, date of first and most recent statin prescription, drug and dosing regimen of initial and final statin prescription, amount of medication patient received during the study period, number of days between first and last statin prescription fill, other drug therapy to serve as surrogate for CHD risk factors or comorbid conditions, and any pertinent side effect comments noted on the patient's prescription profile ("patient allergic to pravastatin - rash"). If the data were missing, they were coded as such ("."). The data were entered both numerically (such as days supply of medication and time

between first and last fill) and categorically (such as drug/dosage, comorbid conditions, and patient comments).

The laboratory portion of CHCS was examined to determine if sufficient LDL lab work was on file. The 1995 PEC Management of Hyperlipidemia guidelines specify that there should be a six-month dose titration period for new patients (with follow-up every two months), then an initial maintenance phase for one year (with follow-up every three months), and the continual maintenance phase (with follow-up every six months).⁶ The labs at the greater San Antonio MTFs use serum as the source for lipoprotein analysis and it is recommended that the lipid panel/profile be drawn in the fasting state. In those patients whose prescription records showed early discontinuation of therapy (such as receiving two statin fills in late 1996 only but continuing to get other prescriptions filled), lab values for liver function tests were obtained in an attempt to determine if side effects as indicated by abnormal labs were possible explanations. Since the Friedewald formula will not work when triglycerides are greater than 400 mg/dl, if chylomicrons are present, or if the patients has Type III hyperlipidemia, the reported LDL value is "0" in these cases. These values were coded as missing (".").

The variables collected depended on availability of recorded labs and included measured total cholesterol, HDL, and triglycerides, as well as calculated values of LDL and cholesterol/HDL ratio. The data were entered based on the timing relationship with the initial statin prescription fill (such as pre-treatment LDL level 1 or 2, post-treatment LDL level at the 2 month, 4 month, 6 month, 9, month, 12 month, etc., PEC guideline recommended intervals). The data were

entered as numerical values. Most labs were not drawn on the exact schedule used by the PEC in their guidelines. The time closest to the target was used as was the mean value in the case of multiple labs (such as the nine month schedule was given as 150 if the eight month value was 200 and the ten month value was 100, but the count for number of labs performed was retained as two for costing purposes for Objective 3). Data were available from August 1995 through April 1998.

Preliminary analysis of the 4436 potential subjects identified by the DUR showed that the majority (3981/4436 or 89.7%) had received one of two drug/dosing regimens: (1) pravastatin 20 mg (3010/4436 or 67.8%); or (2) pravastatin 40 mg (971/4436 or 21.9%). Because of the large number of these two groups of patients and upon the advice of Dr. Karen Rascati, major professor, a random sample of approximately 1/3 of all patients receiving pravastatin 20mg or pravastatin 40mg was selected using the random number seed feature⁷ of the SPSS software, resulting in 1141 pravastatin 20mg patients and 352 pravastatin 40mg patients. There were 23 atorvastatin patients, 59 fluvastatin patients, 23 lovastatin patients, 269 pravastatin 10mg patients, and 81 simvastatin patients in addition to the randomly sampled patients, resulting in 1948 potential subjects.

Patient demographic information was collected on all 4436 patients identified by the DUR. After preliminary screening of the 1948 potential subjects remaining after random selection from the pravastatin 20 mg and 40 mg groups for a minimum of two LDL levels on record, 1412 patients remained. After collecting complete prescription information on these 1412 patients, 492 were found to meet the selection criteria for statin-naive patients. After collecting lab

data on these 492 patients, 289 met the minimum requirement of at least one pre-treatment and post-treatment LDL level on file.

Physician office visits are not specifically coded into this database, but it is usual practice in MTFs that the patient must see a provider for any new prescription or lab order. It was assumed that if the patient had an equal number of prescriptions and lab orders, that these were accomplished during the same provider visits. Otherwise, additional prescriptions or lab orders were counted as additional office visits.

Coding schemes were developed for categories of variables, as appropriate, so that statistical analyses could be performed on a particular variable or in combination with other variables. This was particularly important with the drug/dosing regimen variables. For example, each patient had a record of initial statin received, intermediate statin received, and final statin received. During the study period, therapy may have remained the same, dosing schedule may have changed, or the patient may have switched to another statin. The PEC ran a Statistical Analysis Software (SAS) report for fiscal year 1997 (FY97), October 1, 1996 through September 30, 1997, for the 4436 initially identified patients using patient social security number, patient name, generic drug name, prescription fill date, amount of medication dispensed, days supply, and provider type, which resulted in information on 25,743 prescriptions. Unfortunately, "generic drug name" did not include information on the strength or dosage the patient received, information that was collected manually from CHCS. Therefore, one coding scheme was developed for the full drug/dosing regimen (code 8 meant pravastatin 20 mg tablets, taken twice a day) and another for the

broader drug only category (code 3 meant pravastatin, regardless of whether it was the 10 mg, 20 mg, or 40 mg strength).

DATA ANALYSIS

Demographic Information:

Significance between various patient demographic categories (age, gender, and ethnicity) was tested using *t* tests and Chi-square analyses, as appropriate, between the 4147 subjects who did not meet the selection criteria and the 289 subjects who became the final study subjects (did those selected differ from those not selected).

Objective One:

Objective 1 was to determine whether LDL cholesterol blood levels were being lowered by statin therapy in the actual-use setting of military beneficiaries in the greater San Antonio CHCS population as predicted by the October 1995 PEC guidelines⁶ and/or as predicted by clinical trials.^{8,9} These comparisons were descriptive in nature and compared predicted mean percent reduction in LDL, given as point estimates in the literature, with the observed mean percent reduction in LDL level, with 95 percent confidence intervals calculated, as well as with the percent reduction in LDL level between mean pre-treatment LDL and last recorded LDL, with 95 percent confidence intervals calculated. This was done separately for primary prevention and secondary prevention patients, as well

as contrasting percent LDL reduction between primary and secondary patients by observed mean percent LDL reduction and percent LDL reduction between mean pre-treatment and final LDL level.

The mean percent LDL reduction was calculated using the mean compute transformation¹⁰ in SPSS and then compared as a composite by specific statin used and by specific dosing regimen within a specific statin, as the data allowed. The predicted mean percent LDL reduction point estimates^{6,8,9} were averaged to determine a predicted mean percent reduction in LDL value for each specific statin regardless of strength, using weighting for better estimation (such as for pravastatin -- proportion of 10mg (0.16) times the predicted percent reduction (18.9) + the proportion of pravastatin 20mg (0.70) times the predicted value (23.9) + proportion of pravastatin 40mg (0.14) times the predicted value (33.7) = 24.47 percent as the predicted mean percent reduction in LDL).

An intention to treat and ultimate therapy approach were used to determine which drug/dosing regimen the patient was considered to be on. Intention to treat considers patients to have continued on the initial therapy regardless of whether they actually do so. For this study, a person who initially received pravastatin 10 mg once a day, but later switched to atorvastatin 40 mg twice a day, would be treated as a pravastatin 10 mg once a day patient. With the ultimate therapy approach, the final regimen the patient was on prior to the last LDL level on record was used for analyses. With the previous patient, that would mean treatment as an atorvastatin 40 mg twice a day patient. Objective 1 was tested using both these approaches. Both of these approaches were used primarily to classify patients into drug/dosing regimen categories for analysis purposes.

The literature predicts that primary prevention should demonstrate noticeable LDL reduction at approximately six months, while secondary prevention patients may not show similar results until the two-year point.¹¹ Unfortunately, only one of the final study subjects had LDL values this far after initiation of therapy. While this was a limitation on the mean percent LDL reduction for secondary patients, the majority of the patients were classified as primary prevention patients. Family history of premature CHD and cigarette smoking status are NCEP recognized risk factors for CHD^{12,13} but could not be definitively determined from the fields available in CHCS. Therefore, attainment of NCEP treatment goals for LDL cholesterol levels could not be determined except in a very generalized sense and were not a primary objective of this study.

Objective Two:

Objective 2 was to determine whether there were any differences in this population in percent LDL reduction between the specific statin drugs used. Mostly this consisted of comparing aggregate atorvastatin or fluvastatin or simvastatin against each of the pravastatin dosing regimens and pravastatin as a whole.

It was planned that significance between the mean LDL levels and between baseline and last recorded LDL values would be tested using ANOVA and post hoc techniques. If less than three groups were sufficiently large (having a minimum of 20 subjects per cell), then *t* tests would be used.

Due to the small cell sizes of non-pravastatin subjects, some statistical tests could not be validly performed.

Objective Three:

Objective 3 was to compare the cost-effectiveness of the various statin drug/dosing regimens by calculating mean treatment cost (medication costs, office visit costs, and laboratory test costs) per percent reduction in LDL cholesterol. To estimate costs, yearly usage and expenditure reports maintained by PEC personnel, communications with MTF personnel, and published literature were utilized. Findings were trended at the six, nine, 12, and 18 month points as cell sizes allowed. Cost of treatment was from the MTF viewpoint and focused on direct medical costs of hyperlipidemia treatment. Avoidance of future costs was not addressed here as NCEP patient categories will not be established unequivocally in this retrospective database analysis.

Costs were obtained from the Pharmacoeconomic Center (PEC) in San Antonio, through communication with MTF personnel, and through the literature. Sensitivity analyses were performed holding drug acquisition cost constant and varying office visit costs and lab test costs \pm 20 percent. In summary, this chapter has described how demographic, prescription, and laboratory data were collected from the study population. The selection criteria for final inclusion into the study were discussed as was the elimination process

from the original pool of 4436 potential subjects. The statistical tests ($p < 0.05$) or descriptive techniques used to analyze the data were also discussed.

REFERENCES

1. FDA, Division of Metabolic and Endocrine Drug Products. Guidelines For The Clinical Evaluation of Lipid-Altering Agents In Adults and Children: September, 1990. Rockville, Maryland.
2. CHCS on-line users help menu. February, 1998.
3. Stephen A. Eaker, John P. Kirscht, and Marshall H. Becker, "Understanding and Improving Patient Compliance," *Annals of Internal Medicine* 1984; 100(2): 258-269.
4. Robert Talbert, Personal communication. April 1, 1998.
5. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood cholesterol in Adults (Adult Treatment Panel II). *Journal of the American Medical Association* 1993; 269(23):3015-3023.
6. Pharmacoeconomic Center, PEC Update. 16 October 1995; 96(01):1-A19.
7. SPSS Inc., SPSS® Base 7.5 for Windows User's Guide. SPSS Inc., Chicago, IL, c1997:77.
8. D. Hilleman, et al., Pharmacoeconomic Assessment of HMG-CoA Reductase Inhibitor Therapy: An Analysis Based on the CURVES Study. (Poster presentation at ISPOR Lipid Conference in Orlando, FL; November 4-6, 1997).
9. Sheldon X. Kong, et al., Efficacy of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors in the Treatment of Patients with Hypercholesterolemia: A Meta-Analysis of Clinical Trials. *Clinical Therapeutics* 1997; 19(4):778-797.
10. SPSS Inc., SPSS® Base 7.5 for Windows User's Guide. SPSS Inc., Chicago, IL, c1997:73-76.

11. Vincent Maher, et al., Primary Prevention of Coronary Heart Disease: What Has WOSCOPS Told Us and What Questions Remain? *Drugs* 1997; 54(1):1-8
12. P. W. F. Wilson, et al., Cumulative Effects of High Cholesterol Levels, High Blood Pressure, and Cigarette Smoking on Carotid Stenosis. *New England Journal of Medicine* 1997; 337(8):516-522.
13. G. Howard, et al., Cigarette Smoking and Progression of Atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study. *Journal of the American Medical Association* 1998; 279(2):119-124.

CHAPTER THREE

RESULTS

This chapter contains the findings from the study. Included are results from: (1) Objective 1 - to determine whether LDL cholesterol blood levels are being lowered by statin therapy in the actual-use setting of military beneficiaries in the San Antonio Composite Health Care System (CHCS) computer system as predicted by the October 1995 Pharmacoeconomic Center (PEC)¹ guidelines and/or as predicted by clinical trials;² (2) Objective 2 - to determine whether there are any differences in this population in percent LDL reduction between the specific statin drugs used; and (3) Objective 3 - to compare the cost-effectiveness by calculating treatment cost (medication costs, office visit costs, and laboratory costs, and other related healthcare costs) per percent reduction in LDL cholesterol. The findings are presented in both tabular and textual description format.

ELIMINATION PROCESS

During preliminary research, over 7000 patients were identified as statin users in the San Antonio area by the Composite Health Care System (CHCS) computer system, during the time frame of May 1, 1996 through September 1, 1997. By using drug utilization review (DUR) reports for the periods of October 1-31, 1996, April 1-30, 1997, and October 1-31, 1997, 5382 patients were identified as having received a new statin prescription. After eliminating

duplicate patients, 4436 potential study subjects remained. Preliminary analysis showed the break-down of statin received during the month a patient was identified as follows:

ATORVASTATIN (all strengths)	23	0.5%
FLUVASTATIN (all strengths)	59	1.3%
LOVASTATIN (all strengths)	23	0.5%
PRAVASTATIN (all strengths)	4250	95.8%
SIMVASTATIN (all strengths)	81	1.9%

A further breakdown of those on pravastatin revealed that 269/4250 (6.3%) were on the 10mg dosage, 3010/4250 (70.8%) were on the 20mg dosage, and the remaining 971/4250 (22.9%) were on the 40mg dosage. It was decided to retain all the non-pravastatin patients as well as all the 10mg pravastatin patients for further research, but to randomly select only one-third of the pravastatin 20mg and 40mg patients due to their large proportion of the total sample. This left 1948 potential study patients

The study used percent reduction in low-density lipoprotein (LDL) cholesterol as a surrogate for therapy effectiveness. An initial processing of 599 of the potential study patients revealed that 48.1 percent had pre-treatment lab values recorded, 3.9 percent had pre-treatment labs but were missing LDL values, and 47.9 percent had no pre-treatment labs available at all. Similarly, post-treatment labs were available for 59.2 percent of patients, 3.4 percent had missing

LDL values, and 37.4 percent had no information available. Additionally, 27.4 percent of patients had no lab values of any type available. All remaining potential subjects were screened to insure a minimum of two LDL blood levels on file. After this screening, 1412 patients remained.

To ascertain percent reduction in LDL level following initiation of statin therapy, a minimum of six months of "statin-free" prescription history prior to the initial statin prescription was used. Of the initially processed 599 patients, 44.74 percent (268/599) had less than 90 days of "statin-free" history, 17.03 percent (102/599) had between 91 and 179 days of "statin-free" history, and 38.23 percent (229/599) had 180 or more "statin-free" days on record. Of the 1412 patients having at least two LDL values on file, only 492 could be classified as statin-naive patients.

For final study inclusion, a patient had to not only be a previous non-user of statin drugs, but also meet the minimum selection criteria of having at least one recorded non-zero LDL value both before and after statin therapy was initiated. Of the initially processed 599 patients, only 92 (15.4%) met all this criteria. Of the 492 potential subjects remaining after screening for statin-naive status and a minimum of two LDL values, only 289 had at least one pre- and one post-treatment LDL recorded. These became the final study subjects.

DEMOGRAPHIC INFORMATION FOR SUBJECTS NOT MEETING SELECTION CRITERIA VS FINAL STUDY SUBJECTS

From the original sample of 4436 patients, 4147 were filtered out leaving 289 in the final sample. Comparisons of these groups are shown in Table 3.1. A *t* test indicated that average age was significantly different between the two groups at $p < 0.0001$. Chi-square analysis showed a significant difference in gender between the two groups at $p = 0.019$. Chi-square analysis did not indicate a difference in ethnicity classified as white vs. non-white ($p = 0.326$).

Table 3.1 - Patient Demographics

VARIABLE	SUBJECTS NOT MEETING SELECTION CRITERIA (n = 4147)	SUBJECTS MEETING SELECTION CRITERIA (n = 289)
AGE $p < 0.0001$	Mean of 65.35 (std. dev. 10.28)	Mean of 62.71 (std. dev. 10.78)
GENDER $p = 0.019$	Female 41.3% (1714) Male 58.6% (2429)	Female 34.0% (98) Male 66.0% (191)
ETHNICITY (Reported) $p = 0.326$	White 81.7% (1786) Non-White 18.3% (399)	White 84.6% (159) Non-White 15.4% (29)

For the 4436 in the original sample, the branch of service and family member type were collapsed into broad categories, resulting in the majority of the original sample being 50.4 percent United States Air Force (USAF) retirees and their family members, 26.8 percent United States Army (USA) retirees and their family members, 5.7 percent United States Navy (USN) retirees and their family members, and 3.3 percent USAF active duty and their family members. In the

final study subjects, the majority were USAF retirees and family members (66.4%), followed by USA retirees and family members (19.0%), USAF active duty and family members (6.6%), USN retirees and family members (5.9%), and all other categories (2.1%). Other medical insurance, assuming Medicare for those over 65 years of age, was found in 64.2 percent of the original 4147 subjects versus 53.3 percent in the final subjects. TRICARE PRIME insurance, the military health maintenance organization (HMO) was found in 6.4 percent of the original group and 5.9 percent of the final group. Those reporting no insurance accounted for 14.3 percent and 20.1 percent of the original and final subjects respectively and there was a large number of patients who did not have information recorded for this field (16.0% and 20.8% respectively). Having the home of record listed as out-of-state (all Texas addresses were regarded as in-state) was not common (1.6% and 1.4% respectively).

The results using the final study subjects are reported in the following sections. It should be noted that no lovastatin patients ended up in the final subject group.

OBJECTIVE ONE

To aid in analysis, patients were categorized by prevention type and by statin received both initially and at the conclusion of the DUR. Primary prevention was defined as those without established coronary heart disease (CHD) while those with established CHD (as shown by nitrate usage or admission to inpatient coronary care units) were classified as secondary patients. Drug and

drug/dosing regimen were determined by the particular statin prescribed and the administration directions.

Percent reduction in LDL was calculated using two methods: (1) by averaging the percent LDL reduction over the entire course of therapy; and (2) by comparing the last LDL level recorded to the baseline LDL level. When dosing regimens were collapsed into composite drug categories (all strengths combined), weighting was used to determine predicted point estimates, as described in Chapter Two

INITIAL DRUG AND MEAN % LDL REDUCTION

Table 3.2, classified by initial drug/dosing regimen, shows that by using 95 percent confidence intervals about the calculated mean overall percent LDL reduction, and assuming only those groups with at least 20 subjects are reliable estimates, pravastatin 20mg patients almost attained predicted percent LDL reductions as an overall sample ($18.57\% \pm 3.35$ vs. 23.9%), as primary prevention ($17.48\% \pm 4.53$ vs. 23.9%), and did attain predicted levels as secondary prevention patients ($20.92\% \pm 4.01$ vs. 23.9%). When pravastatin 10mg was dosed as one 10mg tablet daily, the predicted reduction was achieved as an overall sample ($22.41\% \pm 4.33$ vs. 18.9%) and as primary prevention ($22.05\% \pm 5.04$ vs. 18.9%). Pravastatin 40mg did not attain the predicted percent LDL reduction ($5.40\% \pm 13.20$ vs. 33.7%) as an overall sample, and as primary or secondary prevention the individual cells were too small to consider.

Table 3.3 shows that when classified by initial drug alone with all strengths collapsed, none of the statins with at least 20 subjects per group attained predicted mean percent reduction in LDL.

**Table 3.2 Predicted and Observed Mean % LDL Reduction -
Using INITIAL DRUG/DOSING REGIMEN and MEAN OVERALL % LDL
REDUCTION**

DRUG NAME/ DAILY DOSE	PRED. MEAN %REDUC .IN LDL	SAMPLE MEAN % REDUC. IN LDL (N) (95% CI)	PRIMARY PTS. MEAN % (N) (95% CI)	SECONDARY PATIENTS MEAN % (N) (95% CI)
Atorvastatin	N/A	N/A	N/A	N/A
Fluvastatin 20mg	16.8% ^a	9.10% (8) (+11.61)	9.10% (8) (+11.61)	N/A
Pravastatin 10mg - 1x10mg	18.9% ^a	22.41%*(40) (+4.33)	22.05%*(31) (+5.04)	14.31% (9) (+7.49)
Pravastatin 10mg- 1/2x20mg	18.9% ^a	9.60% (1) N/A	N/A	9.60% (1) N/A
Pravastatin 20mg	23.9% ^a	18.57% (193) (+3.35)	17.48% (132) (+4.53)	20.92%* (61) (+4.01)
Pravastatin 40mg - 2x20mg	33.7% ^a	-9.68% (8) (+15.64)	-13.02% (6) (+12.43)	0.35% (2) (+63.38)
Pravastatin 40mg - 1x40mg	33.7% ^a	5.40% (35) (+13.20)	6.82% (19) (+21.82)	3.71% (16) (+13.57)
Simvastatin 10mg	28.2% ^a	-70.86% (1) N/A	N/A	-70.86% (1) N/A
Simvastatin 20mg	35.3% ^a	35.45% (3) (+19.91)	42.87% (2) (+23.56)	20.61% (1) N/A

^a Hilleman (1997)⁴

*Meets predicted percent reduction.

**Table 3.3 Predicted and Observed Mean % LDL Reduction -
Using INITIAL DRUG and MEAN OVERALL % LDL REDUCTION**

DRUG NAME	WTD. PRED. MEAN % REDUC. IN LDL	SAMPLE MEAN % REDUC. IN LDL (N) (95% CI)	PRIMARY PTS. MEAN % (N) (95% CI)	SECONDARY PATIENTS MEAN % (N) (95% CI)
Atorvastatin	N/A	N/A	N/A	N/A
Fluvastatin	16.80%	9.10% (8) (+11.61)	9.10% (8) (+11.61)	N/A
Pravastatin	24.68%	16.31%(277) (+3.05)	16.19%(188) (+4.05)	16.57% (89) (+4.11)
Simvastatin	33.53%	8.87% (4) (+53.96)	42.87% (2) (+23.56)	-25.12% (2) (+89.65)

INITIAL DRUG AND % LDL REDUCTION BETWEEN BASELINE AND LAST RECORDED LDL

When percent LDL reduction was calculated using the difference between the mean pre-treatment LDL level and the last recorded LDL value, slightly different values were obtained. Table 3.4 shows that when classified by initial drug/dosing regimen and using 95 percent confidence intervals, pravastatin 20mg attained the predicted mean percent reduction in LDL of 23.9% in all three categories (20.56% \pm 3.69 as an overall sample, 20.62% \pm 4.72 as primary prevention, and 20.45% \pm 5.73 as secondary prevention). Pravastatin 10mg, with 95 percent confidence intervals, also attained the predicted mean percent LDL reduction of 18.9% when dosed as one 10mg tablet daily (22.43% \pm 5.25 as overall sample and 24.06% \pm 6.44 as primary prevention). Pravastatin 40mg failed to attain the predicted level of 33.7% when dosed as one 40mg tablet daily (4.47% \pm 14.41). No other cells were large enough for meaningful comparisons.

Table 3.5, classified strictly by initial drug prescribed (ignoring the dosing/strength), shows that when using the difference between mean baseline LDL and the final LDL level recorded, pravastatin approached the predicted value of 24.68%, although still falling a bit short in all three categories (18.02% \pm 3.37 as an overall sample, 18.71% \pm 4.33 as primary prevention, and 16.56% \pm 5.13 as secondary prevention).

**Table 3.4 Predicted and Observed Mean % LDL Reduction -
Using INITIAL DRUG/DOSING REGIMEN and % LDL REDUCTION
BETWEEN BASELINE and LAST RECORDED LDL**

DRUG NAME/ DAILY DOSE	WTD. PRED. MEAN % REDUC. IN LDL	SAMPLE % REDUC. IN LDL (N) (95% CI)	PRIMARY PATIENTS MEAN % (N) (95% CI)	SECONDARY PATIENTS MEAN % (N) (95% CI)
Atorvastatin	N/A	N/A	N/A	N/A
Fluvastatin 20mg	16.8% ^a	8.90% (8) (+11.24)	8.90% (8) (+11.24)	N/A
Pravastatin 10mg - 1x10mg	18.9% ^a	22.43%* (40) (+5.25)	24.06%* (31) (+6.44)	16.83% (9) (+6.52)
Pravastatin 10mg- 1/2x20mg	18.9% ^a	9.60% (1) N/A	N/A	9.60% (1) N/A
Pravastatin 20mg	23.9% ^a	20.56%*(193) (+3.69)	20.62%*(132) (+4.72)	20.45%* (61) (+5.73)
Pravastatin 40mg - 2x20mg	33.7% ^a	-5.01% (8) (+19.97)	-7.96% (6) (+19.74)	3.83% (2) (+70.19)
Pravastatin 40mg - 1x40mg	33.7% ^a	4.47% (35) (+14.41)	5.18% (19) (+23.50)	3.63% (16) (+15.56)
Simvastatin 10mg	28.2% ^a	-70.86% (1) N/A	N/A	-70.86% (1) N/A
Simvastatin 20mg	35.3% ^a	35.67% (3) (+27.37)	46.27% (2) (+30.86)	14.47% (1) N/A

^a Hilleman (1997)⁴

*Meets predicted percent LDL reduction.

**Table 3.5 Predicted and Observed Mean % LDL Reduction -
Using INITIAL DRUG and % LDL REDUCTION BETWEEN BASELINE
and LAST RECORDED LDL**

DRUG NAME	WTD. PRED. MEAN% REDUC. IN LDL	SAMPLE % REDUC. IN LDL (N) (95% CI)	PRIMARY PTS. MEAN % (N) (95% CI)	SECONDARY PATIENTS MEAN % (N) (95% CI)
Atorvastatin	N/A	N/A	N/A	N/A
Fluvastatin	16.80%	8.90% (8) (+11.24)	8.90% (8) (+11.24)	N/A
Pravastatin	24.68%	18.02%(277) (+3.37)	18.71%(188) (+4.33)	16.56% (89) (+5.13)
Simvastatin	32.96%	9.04% (4) (+55.67)	46.27% (2) (+30.86)	-28.19% (2) (+83.63)

FINAL DRUG AND MEAN % LDL REDUCTION

Table 3.6, using final drug/dosing regimen and mean overall percent LDL reduction for classification, shows that pravastatin 20mg patients attained the predicted percent LDL reduction of value of 23.9% only in the secondary prevention group ($20.62\% \pm 4.55$). Pravastatin 10mg patients attained the predicted value of 18.9% as an overall sample ($20.48\% \pm 5.58$) and as primary prevention ($21.94\% \pm 6.25$). The only other sufficiently large cells (pravastatin 40mg as an overall sample and as primary prevention) did not attain predicted values ($11.61\% \pm 9.63$ vs. 33.7% and $12.27\% \pm 15.00$, respectively).

Table 3.7, using final drug alone classification, showed that none of the statins attained predicted percent LDL reduction values.

**Table 3.6 Predicted and Observed Mean % LDL Reduction -
FINAL DRUG/DOSING and MEAN OVERALL % LDL REDUCTION**

DRUG NAME AND DAILY DOSE	PRED. MEAN %REDUC. IN LDL	SAMPLE MEAN % Δ IN LDL (N) (95% CI)	PRIMARY PTS. MEAN % Δ (N) (95% CI)	SECONDARY PTS. MEAN % Δ (N) (95% CI)
Atorvastatin 10	38.2% ^a	24.68% (1)	24.68% (1)	N/A
Atorvastatin 20mg	46.3% ^a	-10.35% (2) (+77.59)	29.23% (1) N/A	-49.94% (1) N/A
Atorvastatin 40mg	51.2% ^a	34.34% (2) (+3.25)	N/A	34.34% (2) (+3.25)
Fluvastatin 20mg	16.8% ^a	7.92% (4) (+13.13)	7.92% (7) (+13.13)	N/A
Fluvastatin 40mg	23.0% ^a	17.34% (2) N/A	17.34% (2) N/A	N/A
Pravastatin 10mg	18.9% ^a	20.48%* (25) (+5.58)	21.94%* (21) (+6.25)	9.90% (4) (+9.90)
Pravastatin 20mg x 1/2	18.9% ^a	9.60% (1) N/A	N/A	9.60% (1) N/A
Pravastatin 20mg	23.9% ^a	18.78% (158) (+3.86)	18.00% (111) (+5.16)	20.62%* (47) (+4.55)
Pravastatin 40mg - 2x20mg	33.7% ^a	-8.19% (5) (+18.27)	-8.33% (3) (+19.36)	-7.99% (2) (+47.04)
Pravastatin 40mg - 1x40mg	33.7% ^a	11.61% (45) (+9.63)	12.27% (26) (+15.00)	10.70% (19) (+10.45)
Pravastatin 60mg - 3x20mg	35.7% ^a	35.42% (2) (+29.57)	20.34% (1) N/A	50.51% (1) N/A
Pravastatin 80mg - 2x40mg	37.7% ^b	6.08% (2) (+57.43)	6.08% (2) (+57.43)	N/A
Simvastatin 5mg	22.0% ^c	24.84% (5) (+12.67)	32.74% (3) (+10.34)	12.99% (2) (+19.63)
Simvastatin 10mg	28.2% ^a	-2.56% (4) (+48.91)	20.21% (3) (+28.32)	-70.86% (1) N/A
Simvastatin 20mg	35.3% ^a	0.26% (12) (+19.37)	0.78% (11) (+21.19)	-5.56% (1) N/A
Simvastatin 30mg - 3x10mg	38.2% ^a	30.31% (1) N/A	N/A	30.31% (1) N/A
Simvastatin 40mg - 2x20mg	41.0% ^a	10.63% (1) N/A	N/A	10.63% (1) N/A
Simvastatin 40mg - 1x40mg	41.0% ^a	17.96% (15) (+7.54)	17.41 % (7) (+11.40)	18.44% (8) (+10.75)

^a Hilleman (1997)⁴ ^b Kong (1997)³ ^c Pharmacoeconomic Center (1995)¹ Met level.

**Table 3.7 Predicted and Observed Mean % LDL Reduction -
Using FINAL DRUG and MEAN OVERALL % LDL REDUCTION**

DRUG NAME	WTD. PRED. MEAN % REDUC. IN LDL	SAMPLE MEAN % REDUC. IN LDL (N) (95% CI)	PRIMARY PTS. MEAN % (N) (95% CI)	SECONDARY PATIENTS MEAN % (N) (95% CI)
Atorvastatin	46.64%	14.53% (5) (+31.80)	26.95% (2) (+4.47)	6.25% (3) (+55.10)
Fluvastatin	17.58%	9.10% (8) (+11.61)	9.10% (8) (+11.61)	N/A
Pravastatin	25.63%	17.03% (238) (+3.29)	16.99%(164) (+4.36)	17.13% (74) (+4.36)
Simvastatin	35.28%	11.25% (38) (+8.82)	12.05% (24) (+11.43)	9.86% (14) (+14.28)

FINAL DRUG AND % LDL REDUCTION BETWEEN BASELINE AND LAST RECORDED LDL

Table 3.8, using final drug/dosing regimen as classification, shows that, when the difference between mean pre-treatment LDL level and last recorded LDL level are used to represent mean percent reduction in LDL, pravastatin 10mg and 20mg regimens attain predicted values as overall samples ($21.44\% \pm 5.77$ vs. 18.9% and $20.09\% \pm 4.21$ vs. 23.9% , respectively) and as primary prevention ($23.08\% \pm 6.44$ vs. 18.9% and $20.35\% \pm 5.33$ vs. 23.9% , respectively). Pravastatin 20mg patients also attained the predicted value of 23.9% as secondary prevention ($19.47\% \pm 6.59$). Pravastatin 40mg did not attain the predicted values of 33.7% despite sufficient cell size.

Table 3.9, using final drug prescribed as classification and difference between baseline LDL value and last recorded LDL value, shows that pravastatin patients as a group approached the predicted value of 25.62% as an overall sample and as primary prevention, but did not attain it ($18.06\% \pm 3.66$ as overall sample and $19.26\% \pm 4.65$ as primary prevention). Despite sufficient cell size, pravastatin secondary prevention patients ($15.41\% \pm 5.70$ vs. 25.63%), simvastatin as an overall sample ($15.71\% \pm 9.35$ vs. 38.28%) and simvastatin primary prevention patients ($14.82\% \pm 11.95$ vs. 38.28%) did not attain the predicted values.

**Table 3.8 Predicted and Observed Mean % LDL Reduction -
FINAL DRUG/DOSING and % LDL REDUCTION BASELINE/LAST LDL**

DRUG NAME/ DAILY DOSE	PRED. MEAN % REDUC. IN LDL	SAMPLE % Δ IN LDL (N) (95% CI)	PRIMARY PTS. MEAN % Δ (N) (95% CI)	SECONDARY PTS. MEAN % Δ (N) (95% CI)
Atorvastatin 10	38.2% ^a	62.60% (1)	62.60% (1)	N/A
Atorvastatin 20mg	46.3% ^a	-3.16% (2) (+72.22)	33.69% (1) N/A	-40.00% (1) N/A
Atorvastatin 40mg	51.2% ^a	37.82% (2) (+3.56)	N/A	37.82% (2) (+3.56)
Fluvastatin 20mg	16.8% ^a	7.12% (7) (+12.33)	7.12% (7) (+12.33)	N/A
Fluvastatin 40mg	23.0% ^a	21.39% (1) N/A	21.39% (1) N/A	N/A
Pravastatin 10mg	18.9% ^a	21.39%* (25) (+5.77)	23.08%* (21) (+6.44)	12.81% (4) (+9.90)
Pravastatin 20mgx1/2	18.9% ^a	9.60% (1) N/A	N/A	9.60% (1) N/A
Pravastatin 20mg	23.9% ^a	20.09%*(132) (+4.21)	20.35%*(111) (+5.33)	19.47%* (47) (+6.59)
Pravastatin 40mg - 2x20mg	33.7% ^a	-7.73% (5) (+16.40)	-8.97% (3) (+3.91)	-5.86% (2) (+51.20)
Pravastatin 40mg - 1x40mg	33.7% ^a	11.45% (45) (+11.34)	15.41% (26) (+17.40)	6.04% (19) (+12.59)
Pravastatin 60mg - 3x20mg	35.7% ^a	38.00% (2) (+46.20)	14.43% (1) N/A	61.57% (1) N/A
Pravastatin 80mg - 2x40mg	37.7% ^b	13.52% (2) (+48.00)	13.52% (2) (+48.00)	N/A
Simvastatin 5mg	22.0% ^c	24.83% (5) (+12.59)	30.35% (3) (+18.80)	16.32% (2) (+7.79)
Simvastatin 10mg	28.2% ^a	-4.93% (4) (+54.80)	17.05% (3) (+47.91)	-70.86% (3) N/A
Simvastatin 20mg	35.3% ^a	4.15% (12) (+18.53)	3.67% (11) (+20.27)	9.40% (1) N/A
Simvastatin 30mg - 3x10mg	38.2% ^a	48.12% (1) N/A	N/A	48.12% (1) N/A
Simvastatin 40mg - 2x20mg	41.0% ^a	22.41% (1) N/A	N/A	22.41% (1) N/A
Simvastatin 40mg	41.0% ^a	24.83% (15) (+8.46)	24.67% (7) (+12.91)	24.96% (8) (+11.98)

^a Hilleman (1997)⁴ ^b Kong (1997)³ ^c Pharmacoeconomic Center (1995)¹ *Met level

**Table 3.9 Predicted and Observed Mean % LDL Reduction -
Using FINAL DRUG and % LDL REDUCTION BETWEEN BASELINE
and LAST RECORDED LDL**

DRUG NAME	WTD. PRED. MEAN % REDUC. IN LDL	SAMPLE % REDUC. IN LDL (N) (95% CI)	PRIMARY PTS. MEAN % (N) (95% CI)	SECONDARY PATIENTS MEAN % (N) (95% CI)
Atorvastatin	46.64%	26.38% (5) (+34.06)	48.14% (2) (+28.33)	11.88% (3) (+50.88)
Fluvastatin	17.58%	8.90% (8) (+11.24)	8.90% (8) (+11.24)	N/A
Pravastatin	25.63%	18.06%(238) (+3.66)	19.26%(164) (+4.65)	15.41% (74) (+5.70)
Simvastatin	38.28%	15.71% (38) (+9.35)	14.82% (24) (+11.95)	17.24% (14) (+15.52)

OBJECTIVE TWO

Comparisons between the different statins were performed using the classifications of primary prevention, secondary prevention, and overall sample, as well as by drug and whether the drug was the initial or final one prescribed. Statistical comparisons were limited by numerous small cell sizes.

INITIAL DRUG AS CLASSIFICATION

Table 3.10, using initial drug as classification, shows that whether mean percent reduction in LDL or the percent reduction between baseline and last recorded LDL are used, as an overall sample none of the three statins attained predicted values. Pravastatin approached the predicted value of 24.68%, but did not attain it with the use of 95 percent confidence intervals. Tables 3.11 and 3.12 show similar results for primary prevention and secondary prevention patients. ANOVA techniques were not used because of small and unbalanced cell sizes.

**Table 3.10 Observed Changes in LDL Cholesterol Levels - SAMPLE
OVERALL - Using INITIAL Drug Prescribed**

DRUG NAME	BASELINE LDL (mg/dl)	WTD. PRED. % LDL CHANGE	MEAN % CHANGE IN LDL	% LDL CHANGE BETWEEN BASELINE / LAST LDL
<u>ATORVASTATIN</u>	N/A	N/A	N/A	N/A
<u>FLUVASTATIN</u> (n = 8)				
Mean	179.44	16.80%	9.10%	8.90%
(95% CI)	+13.19		+11.61	+11.24
Median	175		16.05%	15.56%
Range	65		50	48
<u>PRAVASTATIN</u> (n = 277)				
Mean	148.17	24.68%	16.31%	18.02%
(95% CI)	+4.57		+3.05	+3.37
Median	148		21.74%	23.25
Range	205		231	286
<u>SIMVASTATIN</u> (n = 4)				
Mean	140.13	33.53%	8.87%	9.04%
(95% CI)	+43.90		+53.96	+55.67
Median	153		25.73%	22.50%
Range	104		126	133

Statistical tests not done because of small and unbalanced cell sizes.

Table 3.11 Observed Changes in LDL Cholesterol Levels - PRIMARY PREVENTION - Using INITIAL Drug Prescribed

DRUG NAME	BASELINE LDL (mg/dl)	WTD. PRED. % LDL CHANGE	MEAN % CHANGE IN LDL	% LDL CHANGE BETWEEN BASELINE / LAST LDL
<u>ATORVASTATIN</u>	N/A	N/A	N/A	N/A
<u>FLUVASTATIN</u> (n = 8)				
Mean	179.44	16.80%	9.10%	8.90%
(95% CI)	+13.19		+11.61	+11.24
Median	175		16.05%	15.56%
Range	65		50	48
<u>PRAVASTATIN</u> (n = 188)				
Mean	153.46	24.68%	16.19%	18.71%
(95% CI)	+5.61		+4.05	+4.33
Median	156		22.16%	25.17%
Range	205		227	286
<u>SIMVASTATIN</u> (n = 2)				
Mean	166.50	33.53%	42.87%	46.27%
(95% CI)	+24.50		+23.56	+30.86
Median	166		42.87%	46.27%
Range	25		24	31

Statistical tests not done because of small and unbalanced cell sizes.

Table 3.12 Observed Changes in LDL Cholesterol Levels - SECONDARY PREVENTION - Using INITIAL Drug Prescribed

DRUG NAME	BASELINE LDL (mg/dl)	WTD. PRED. % LDL CHANGE	MEAN % CHANGE IN LDL	% LDL CHANGE BETWEEN BASELINE / LAST LDL
<u>ATORVASTATIN</u>	N/A	N/A	N/A	N/A
<u>FLUVASTATIN</u> (n = 0) Mean (95% CI) Median Range	N/A	16.80%	N/A	N/A
<u>PRAVASTATIN</u> (n = 89) Mean (95% CI) Median Range	136.98 ±7.47 132 169	24.68%	16.57% ±4.11 18.25% 118	16.56% ±5.13 21.89% 144
<u>SIMVASTATIN</u> (n = 2) Mean (95% CI) Median Range	113.75 ±74.97 114 77	33.53%	-25.12% ±89.65 -25.12% 91	-28.19% ±83.63 -28.19% 85

Statistical tests not done because of small and unbalanced cell sizes.

FINAL DRUG AS CLASSIFICATION

Table 3.13, using final drug prescribed as classification, shows that pravastatin as an overall sample approached the predicted value of 25.63% using the difference between baseline and last recorded LDL value ($18.06\% \pm 3.66$) while the mean overall percent reduction was not as close ($17.03\% \pm 3.29$). Simvastatin did not come close to the predicted value of 35.29% by either calculation method ($11.25\% \pm 8.82$ for mean percent change and $15.71\% \pm 9.35$ for the baseline to last LDL change). Due to small and unbalanced cell sizes, statistical tests could only be used to compare pravastatin and simvastatin patients as composites. Using *t* test techniques and assuming unequal variances, no significant differences were detected for mean percent change ($p = 0.235$) or for the baseline to last LDL change ($p = 0.649$).

**Table 3.13 Observed Changes in LDL Cholesterol Levels - SAMPLE
OVERALL - Using FINAL Drug Prescribed**

DRUG NAME	BASELINE LDL (mg/dl)	WTD. PRED. % LDL CHANGE	MEAN % CHANGE IN LDL	% LDL CHANGE BETWEEN BASELINE / LAST LDL
<u>ATORVASTATIN</u> (n = 5)				
Mean	147.40	46.64%	14.53%	26.38%
(95% CI)	+36.53		+31.80	+34.06
Median	138		29.23%	36.00%
Range	98		86	103
<u>FLUVASTATIN</u> (n = 8)				
Mean	179.44	17.58%	9.10%	8.90%
(95% CI)	+13.19		+11.61	+11.24
Median	175		16.05%	15.56%
Range	65		50	48
<u>PRAVASTATIN</u> (n = 238)				
Mean	147.58	25.63%	17.03%	18.06%
(95% CI)	+4.92		+3.29	+3.66
Median	148		21.93%	23.41%
Range	205		231	286
<u>SIMVASTATIN</u> (n = 38)				
Mean	151.12	35.28%	11.25%	15.71%
(95% CI)	+12.70		+8.82	+9.35
Median	151		15.78%	22.12%
Range	162		134	133

T tests done for pravastatin and simvastatin only due to small and unbalance cell sizes.

Table 3.14, using final drug prescribed as classification, shows that as primary prevention, pravastatin approaches the predicted value of 25.63% using baseline to last LDL calculations ($19.26\% \pm 4.66$) but not as closely using mean overall percent reduction in LDL ($16.99\% \pm 4.36$). Again, a *t* test indicated that there were no statistically significant differences between the pravastatin and simvastatin groups (for mean percent change $p = 0.436$ and for baseline to last LDL change $p = 0.503$).

Table 3.15, using final drug prescribed as classification, shows that none of the drugs attained predicted values in secondary prevention patients, although pravastatin approached the predicted value of 25.63 percent using both calculation approaches ($17.13\% \pm 4.36$ for mean percent change and $15.41\% \pm 5.70$ for baseline to last LDL change. Cell sizes were too small to use statistical analysis.

**Table 3.14 Observed Changes in LDL Cholesterol Levels - PRIMARY
PREVENTION - Using FINAL Drug Prescribed**

DRUG NAME	BASELINE LDL (mg/dl)	WTD. PRED. % LDL CHANGE	MEAN % CHANGE IN LDL	% LDL CHANGE BETWEEN BASELINE / LAST LDL
<u>ATORVASTATIN</u> (n = 2)				
Mean	189.75	46.64%	26.95%	48.14%
(95% CI)	+5.39		+4.47	+28.33
Median	190		26.95%	48.14%
Range	6		5	29
<u>FLUVASTATIN</u> (n = 8)				
Mean	179.44	17.58%	9.10%	8.90%
(95% CI)	+13.19		+11.61	+11.24
Median	175		16.05%	15.56%
Range	65		50	48
<u>PRAVASTATIN</u> (n = 164)				
Mean	152.81	25.63%	16.99%	19.26%
(95% CI)	+5.88		+4.36	+4.66
Median	156		22.04%	25.66%
Range	205		226	286
<u>SIMVASTATIN</u> (n = 24)				
Mean	155.98	35.28%	12.05%	14.82%
(95% CI)	+17.37		+11.43	+11.95
Median	157		19.13%	19.71%
Range	152		135	120

T tests done for pravastatin and simvastatin only due to small and unbalance cell sizes.

Table 3.15 Observed Changes in LDL Cholesterol Levels - SECONDARY PREVENTION - Using FINAL Drug Prescribed

DRUG NAME	BASELINE LDL (mg/dl)	WTD. PRED. % LDL CHANGE	MEAN % CHANGE IN LDL	% LDL CHANGE BETWEEN BASELINE / LAST LDL
<u>ATORVASTATIN</u> (n = 3) Mean (95% CI) Median Range	119.17 +24.34 125 43	46.64%	6.25% +55.10 32.69% 86	11.88% +50.88 36.00% 80
<u>FLUVASTATIN</u> (n = 0) Mean (95% CI) Median Range	N/A	17.58%	N/A	N/A
<u>PRAVASTATIN</u> (n = 74) Mean (95% CI) Median Range	135.98 +8.47 130 169	25.63%	17.31% +4.36 19.25% 109	15.41% +5.70 20.57% 144
<u>SIMVASTATIN</u> (n = 14) Mean (95% CI) Median Range	142.79 +17.25 140 138	35.28%	9.86% +14.28 14.67% 118	17.24% +15.52 22.12% 132

Statistical tests not done because of small and unbalanced cell sizes.

OBJECTIVE THREE

Total direct medical costs were estimated for drug acquisition cost, healthcare provider office visit cost, and lab value costs. Drug acquisition cost was calculated by summing up the total cost (actual number of tablets of each statin received times the cost per tablet, excluding the final statin fill) of all statins dispensed to each patient during the study period, divided by the number of days between the first and last statin prescription, and then multiplied by 365 to estimate annual costs. Office visits were calculated by multiplying the number of prescriptions or the number of post-treatment lipid panels, whichever was greater, by \$31.25 (it was assumed that if the patient received an equal number of prescriptions and labs, the same office visit generated both, so only \$31.25 times the number of prescriptions was used). Pre-treatment labs were excluded as they represented diagnostic costs and not treatment costs. This value was then divided by the number of days between first and last statin prescription fill and multiplied by 365 to estimate annual costs. Lab costs were calculated similarly with \$56.00 assigned to each lipid panel (total cholesterol, high-density lipoprotein cholesterol, and triglycerides directly measured and LDL calculated) which is how the LDL lab values are obtained. Labs required to detect side effects or adverse events were priced at \$1.65 each (the military cost to add the two liver function tests ALT (alanine aminotransferase) or GGT (gamma glutamyl transferase) to routine blood work). Extra office visit costs were not generated by side effect labs as they were add-on labs for routine lab work, not a special request as the lipid panels were.

INITIAL DRUG/DOSE AS CLASSIFICATION

Table 3.16, using initial drug/dosing regimens as classification, shows the overall sample calculations for total estimated direct medical costs using mean drug acquisition costs, mean office visit costs, and mean lab test costs. Mean drug acquisition costs ranged from a low of \$335.60 for pravastatin 20mg to a high of \$557.51 for pravastatin 40mg, when a minimum cell size of 20 was used. Otherwise, these costs ranged from a low of \$263.10 for one pravastatin 1/2 x 20mg patient to a high of \$525.79 for eight pravastatin 2 x 20mg patients. Mean office visit costs ranged from \$139.89 for pravastatin 20mg patients to \$220.05 for pravastatin 10mg patients (minimum cell size of 20). Otherwise, the minimum mean annual office visit cost was \$96.59 for eight patient receiving pravastatin 20mg, two tablets daily, and the maximum mean annual office visit cost was for the eight fluvastatin 20mg patients at \$178.91. Mean lab test costs ranged from \$184.39 for pravastatin 20mg patients to \$255.68 for pravastatin 10mg patients (cell size minimum of 20). Otherwise, these costs ranged from \$56.78 for one patient receiving pravastatin 20mg, one-half tablet daily, to the aforementioned eight fluvastatin 20mg patients at \$222.66. Total estimated direct medical costs ranged from \$659.88 for the pravastatin 20mg group to \$964.02 for the pravastatin 10mg group (minimum cell size of 20). Otherwise, these costs ranged from \$446.62 for the one pravastatin, one-half by 20mg tablet< patient to \$795.09 for the one simvastatin 10mg patient.

Table 3.16 Annual Cost Estimates of Treatment - SAMPLE OVERALL
Using INITIAL DRUG/DOSING REGIMEN and Mean Costs

DRUG NAME AND DAILY DOSE	DRUG ACQ. COSTS (\$)	OFFICE VISIT COSTS (\$)	LAB TEST COSTS (\$)	TOTAL DIR. MED. COSTS (\$)
Atorvastatin 10mg (n = 0)	N/A	N/A	N/A	N/A
Atorvastatin 20mg (n = 0)	N/A	N/A	N/A	N/A
Atorvastatin 40mg (n = 0)	N/A	N/A	N/A	N/A
Fluvastatin 20mg (n = 8)	290.14	178.91	222.66	691.71
Fluvastatin 40mg (n = 0)	N/A	N/A	N/A	N/A
Pravastatin 10mg (n = 40) 1 x 10mg	366.02	220.05	255.68	841.75
Pravastatin 10mg (n = 1) 1/2 x 20mg	263.10	126.74	56.78	446.62
Pravastatin 20mg (n = 193)	335.60	139.89	184.39	659.88
Pravastatin 40mg (n = 8) 2 x 20mg	525.79	96.59	132.29	754.67
Pravastatin 40mg (n = 35) 1 x 40mg	557.51	178.48	228.03	964.02
Pravastatin 60mg (n = 0) 3 x 20mg	N/A	N/A	N/A	N/A
Pravastatin 80mg (n = 0) 2 x 40mg	N/A	N/A	N/A	N/A
Simvastatin 5mg (n = 0)	N/A	N/A	N/A	N/A
Simvastatin 10mg (n = 1)	430.70	228.12	136.27	795.09
Simvastatin 20mg (n = 3)	499.34	103.50	189.49	792.33
Simvastatin 30mg (n = 0) 3 x 10mg	N/A	N/A	N/A	N/A
Simvastatin 40mg (n = 0) 2 x 20mg	N/A	N/A	N/A	N/A

Table 3.17, using initial drug/dosing regimen as classification, shows estimated annual total direct medical costs for the primary prevention patients. Only six different drug/dosing regimens were initially prescribed for the study patients. Only pravastatin 10mg and 20mg had a cell size over 20. Pravastatin 10mg had mean estimated annual drug costs of \$386.24, mean estimated annual office visit costs of \$245.88, and mean estimated annual lab test costs of \$276.96, for total estimated annual direct medical costs of \$909.05. Pravastatin 20mg had drug costs of \$324.45, office visit costs of \$145.04, and lab test costs of \$190.47, for total estimated annual direct medical costs of \$659.96. From the remaining smaller cells, the minimum total estimated medical costs were \$663.26 for the six pravastatin two by 20mg daily patients and a maximum total estimated annual medical costs of \$1010.07 for the group with 19 pravastatin 40mg, once daily patients.

**Table 3.17 Annual Cost Estimates of Treatment - PRIMARY
PREVENTION Using INITIAL DRUG/DOSING and Mean Costs**

DRUG NAME AND DAILY DOSE	DRUG ACQ. COSTS (\$)	OFFICE VISIT COSTS (\$)	LAB TEST COSTS (\$)	TOTAL DIR. MED. COSTS (\$)
Atorvastatin 10mg (n = 0)	N/A	N/A	N/A	N/A
Atorvastatin 20mg (n = 0)	N/A	N/A	N/A	N/A
Atorvastatin 40mg (n = 0)	N/A	N/A	N/A	N/A
Fluvastatin 20mg (n = 8)	290.14	178.91	222.66	691.71
Fluvastatin 40mg (n = 0)	N/A	N/A	N/A	N/A
Pravastatin 10mg (n = 31) 1 x 10mg	386.24	245.88	276.93	909.05
Pravastatin 10mg (n = 0) 1/2 x 20mg	N/A	N/A	N/A	N/A
Pravastatin 20mg (n = 132)	324.45	145.04	190.47	659.96
Pravastatin 40mg (n = 6) 2 x 20mg	457.87	87.87	117.52	663.26
Pravastatin 40mg (n = 19) 1 x 40mg	575.88	172.16	262.03	1010.07
Pravastatin 60mg (n = 0) 3 x 20mg	N/A	N/A	N/A	N/A
Pravastatin 80mg (n = 0) 2 x 40mg	N/A	N/A	N/A	N/A
Simvastatin 5mg (n = 0)	N/A	N/A	N/A	N/A
Simvastatin 10mg (n = 0)	N/A	N/A	N/A	N/A
Simvastatin 20mg (n = 2)	399.22	104.56	187.37	691.15
Simvastatin 30mg (n = 0) 3 x 10mg	N/A	N/A	N/A	N/A
Simvastatin 40mg (n = 0) 2 x 20mg	N/A	N/A	N/A	N/A

Table 3.18, using initial drug/dosing regimen as classification, shows the annual cost estimates for treatment of secondary prevention patients. Only the pravastatin 20mg patient group had a sufficient cell size (61) for reliable estimations. For this group, the total estimated annual direct medical costs of \$659.72 were calculated from mean estimated annual drug costs of \$359.73, mean estimated annual office visit costs of \$128.75, and mean estimated annual lab test costs of \$171.24. The minimum and maximum estimated total annual direct medical costs for the remaining smaller groups were \$609.97 for the nine pravastatin 10mg, one tablet daily, patients and \$1028.94 for the two pravastatin two by 20mg tablets daily, patients.

Table 3.18 Annual Cost Estimates of Treatment - SECONDARY PREVENTION Using INITIAL DRUG/DOSING and Mean Costs

DRUG NAME AND DAILY DOSE	DRUG ACQ. COSTS (\$)	OFFICE VISIT COSTS (\$)	LAB TEST COSTS (\$)	TOTAL DIR. MED. COSTS (\$)
Atorvastatin 10mg (n = 0)	N/A	N/A	N/A	N/A
Atorvastatin 20mg (n = 0)	N/A	N/A	N/A	N/A
Atorvastatin 40mg (n = 0)	N/A	N/A	N/A	N/A
Fluvastatin 20mg (n = 0)	N/A	N/A	N/A	N/A
Fluvastatin 40mg (n = 0)	N/A	N/A	N/A	N/A
Pravastatin 10mg (n = 9) 1 x 10mg	296.38	131.09	182.50	609.97
Pravastatin 10mg (n = 1) 1/2 x 20mg	263.10	126.74	56.78	446.62
Pravastatin 20mg (n = 61)	359.73	128.75	171.24	659.72
Pravastatin 40mg (n = 2) 2 x 20mg	729.54	122.78	176.62	1028.94
Pravastatin 40mg (n = 16) 1 x 40mg	535.69	185.97	187.65	909.31
Pravastatin 60mg (n = 0) 3 x 20mg	N/A	N/A	N/A	N/A
Pravastatin 80mg (n = 0) 2 x 40mg	N/A	N/A	N/A	N/A
Simvastatin 5mg (n = 0)	N/A	N/A	N/A	N/A
Simvastatin 10mg (n = 1)	430.70	228.12	136.27	795.09
Simvastatin 20mg (n = 1)	699.58	101.39	193.73	994.70
Simvastatin 30mg (n = 0) 3 x 10mg	N/A	N/A	N/A	N/A
Simvastatin 40mg (n = 0) 2 x 20mg	N/A	N/A	N/A	N/A

INITIAL DRUG ALONE AS CLASSIFICATION

Table 3.19 through Table 3.21, using initial drug alone as classification, show annual cost estimates of treatment for sample overall, primary prevention, and secondary prevention patients. Only the pravastatin groups had sufficiently large cell sizes, of 277, 188, and 89, respectively, for further consideration. The overall sample of pravastatin had total estimated annual direct medical costs of \$726.54. The primary prevention patients' estimate of annual total direct medical costs was \$736.52. The secondary prevention patients' estimate was \$705.47. From the combination of all three tables, the lowest estimate of annual total direct medical cost for the smaller sized cells was for the two primary prevention simvastatin patients at \$691.15 and the highest total estimate was \$894.90 for the two secondary prevention simvastatin patients.

Table 3.19 Annual Cost Estimates of Treatment - SAMPLE OVERALL
Using INITIAL DRUG and Mean Costs

DRUG NAME	DRUG ACQ. COSTS (\$)	OFFICE VISIT COSTS (\$)	LAB TEST COSTS (\$)	TOTAL DIR. MED. COSTS (\$)
Atorvastatin (n = 0)	N/A	N/A	N/A	N/A
Fluvastatin (n = 8)	290.14	178.91	222.66	691.71
Pravastatin (n = 277)	373.26	155.04	198.24	726.54
Simvastatin (n = 4)	482.18	134.66	176.18	793.02

**Table 3.20 Annual Cost Estimates of Treatment - PRIMARY
PREVENTION Using INITIAL DRUG and Mean Costs**

DRUG NAME	DRUG ACQ. COSTS (\$)	OFFICE VISIT COSTS (\$)	LAB TEST COSTS (\$)	TOTAL DIR. MED. COSTS (\$)
Atorvastatin (n = 0)	N/A	N/A	N/A	N/A
Fluvastatin (n = 8)	290.14	178.91	222.66	691.71
Pravastatin (n = 188)	364.31	162.58	209.63	736.52
Simvastatin (n = 2)	399.22	104.56	187.37	691.15

**Table 3.21 Annual Cost Estimates of Treatment - SECONDARY
PREVENTION Using INITIAL DRUG and Mean Costs**

DRUG NAME	DRUG ACQ. COSTS (\$)	OFFICE VISIT COSTS (\$)	LAB TEST COSTS (\$)	TOTAL DIR. MED. COSTS (\$)
Atorvastatin (n = 0)	N/A	N/A	N/A	N/A
Fluvastatin (n = 0)	N/A	N/A	N/A	N/A
Pravastatin (n = 89)	392.18	139.12	174.17	705.47
Simvastatin (n = 2)	565.14	164.76	165.00	894.90

FINAL DRUG/DOSE AS CLASSIFICATION

Annual estimated total direct medical costs were also calculated using the final drug/dosing regimen prescribed for the final study patients. Table 3.22 shows annual total direct medical cost estimates for the 18 different drug/dosing regimens found in the overall sample, classified by final therapy. Only three regimens met the requirements for a minimum cell size of 20. Pravastatin 20mg, once daily, had a cell size of 158, pravastatin 40mg, once daily, had a cell size of 45, and pravastatin 10mg, one 10mg tablet daily, had a cell size of 25. Estimated total annual direct medical costs were lowest for the pravastatin 20mg patients at \$634.67 and highest for the pravastatin 40mg patients at \$899.76. The mean annual estimated drug acquisition costs for these three groups ranged from a low of \$301.95 for the pravastatin 20mg patients to a high of \$509.52 for the pravastatin 40mg patients. The pravastatin 10mg patients had drug costs of \$337.84. The mean annual estimated office visit costs for these three groups ranged from a low of \$146.24 for the pravastatin 20mg patients to a high of \$200.05 for the pravastatin 10mg patients. The mean annual estimated lab costs for the three groups meeting the minimum requirement of 20 subjects per cell ranged from a low of \$186.48 for the pravastatin 20mg patients to a high of \$228.20 for the pravastatin 10mg patients.

For the groups not meeting the minimum cell size requirement of 20, the lowest total estimated annual direct medical costs were for the one atorvastatin 10mg patient at \$534.72 and the highest were for the one simvastatin two by 20mg patient at \$1300.26. The lowest mean estimated annual drug acquisition

costs were for the one atorvastatin 10mg patient at \$234.33 and the highest drug costs were for the one simvastatin two by 20mg patient at \$971.51. The lowest and highest mean estimated annual office visit costs were \$107.18 for the pravastatin 20mg twice daily patients and \$242.38 for the ten simvastatin 10mg patients. The highest and lowest mean estimated annual lab test costs were \$130.40 for the two atorvastatin 40mg patients and \$420.88 for the one fluvastatin 40mg patient.

Table 3.22 Annual Cost Estimates of Treatment - SAMPLE OVERALL
Using FINAL DRUG/DOSING REGIMEN and Mean Costs

DRUG NAME AND DAILY DOSE	DRUG ACQ. COSTS (\$)	OFFICE VISIT COSTS (\$)	LAB TEST COSTS (\$)	TOTAL DIR. MED. COSTS (\$)
Atorvastatin 10mg (n = 1)	234.33	152.08	148.31	534.72
Atorvastatin 20mg (n = 2)	474.19	123.81	201.82	799.82
Atorvastatin 40mg (n = 2)	790.16	122.78	130.40	1043.34
Fluvastatin 20mg (n = 7)	282.72	173.43	194.34	650.49
Fluvastatin 40mg (n = 1)	342.06	217.26	420.88	980.20
Pravastatin 10mg (n = 25) 1 x 10mg	337.84	200.05	228.20	766.09
Pravastatin 10mg (n = 1) 1/2 x 20mg	263.10	126.74	56.78	446.62
Pravastatin 20mg (n = 158)	301.95	146.24	186.48	634.67
Pravastatin 40mg (n = 5) 2 x 20mg	480.76	107.18	160.31	748.25
Pravastatin 40mg (n = 45) 1 x 40mg	509.52	173.05	217.19	899.76
Pravastatin 60mg (n = 2) 3 x 20mg	593.53	174.73	300.16	1068.42
Pravastatin 80mg (n = 2) 2 x 40mg	792.29	161.59	193.04	1146.92
Simvastatin 5mg (n = 5)	253.22	155.46	199.78	608.46
Simvastatin 10mg (n = 4)	623.40	242.38	380.02	1245.80
Simvastatin 20mg (n = 12)	433.24	129.90	184.44	747.58
Simvastatin 30mg (n = 1) 3 x 10mg	308.22	168.98	227.11	704.31
Simvastatin 40mg (n = 1) 2 x 20mg	971.51	158.42	170.33	1300.26
Simvastatin 40mg (n = 15) 1 x 40mg	520.06	131.87	192.48	844.41

Table 3.23, using final drug/dosing regimen as classification, shows the annual cost estimates of treatment for the primary prevention patients. Only three of the pravastatin sub-groups met the requirement of a minimum cell size of 20 patients. Pravastatin 10mg, 20mg, and 40mg (once daily) had estimated total annual direct medical costs of \$800.97, \$655.30, and \$909.43, respectively. The mean estimated annual drug acquisition costs were \$346.06 for the pravastatin 10mg patients, \$309.06 for the pravastatin 20mg patients, and \$498.21 for pravastatin 40mg patients. Mean estimated annual office visit costs ranged from \$155.33 for the pravastatin 20mg patients to \$211.51 for the pravastatin 10mg patients. Mean estimated annual lab test costs ranged from \$190.91 for pravastatin 20mg patients to \$243.40 for pravastatin 10mg patients.

For the remaining groups not meeting the minimum cell size requirement, the lowest estimated total annual direct medical costs were \$534.72 for the one atorvastatin 10mg patient and the highest were for the three simvastatin 10mg patients at \$1396.05. Mean estimated annual drug acquisition costs ranged from a low of \$234.33 for the atorvastatin 10mg patient to a high of \$687.64 for the three simvastatin 10mg patients. Mean estimated annual office visit costs ranged from a low of \$94.15 for the three pravastatin two by 20mg patients to a high of \$247.14 for the three simvastatin 10mg patients. Mean estimated annual lab test costs ranged from \$148.31 for the atorvastatin 10mg patient to \$461.27 for the three simvastatin 10mg patients.

Table 3.23 Annual Cost Estimates of Treatment - PRIMARY PREVENTION
Using FINAL DRUG/DOSING REGIMEN and Mean Costs

DRUG NAME AND DAILY DOSE	DRUG ACQ. COSTS (\$)	OFFICE VISIT COSTS (\$)	LAB TEST COSTS (\$)	TOTAL DIR. MED. COSTS (\$)
Atorvastatin 10mg (n = 1)	234.33	152.08	148.31	534.72
Atorvastatin 20mg (n = 1)	512.72	111.83	160.31	784.86
Atorvastatin 40mg (n = 0)	N/A	N/A	N/A	N/A
Fluvastatin 20mg (n = 7)	282.72	173.43	194.35	650.50
Fluvastatin 40mg (n = 1)	342.06	217.26	420.88	980.20
Pravastatin 10mg (n = 21) 1 x 10mg	346.06	211.51	243.40	800.97
Pravastatin 10mg (n = 0) 1/2 x 20mg	N/A	N/A	N/A	N/A
Pravastatin 20mg (n = 111)	309.06	155.33	190.91	655.30
Pravastatin 40mg (n = 3) 2 x 20mg	460.60	94.15	174.98	729.73
Pravastatin 40mg (n = 26) 1 x 40mg	498.21	169.54	241.68	909.43
Pravastatin 60mg (n = 1) 3 x 20mg	542.94	237.63	425.83	1206.40
Pravastatin 80mg (n = 2) 2 x 40mg	792.29	161.59	193.04	1146.92
Simvastatin 5mg (n = 3)	263.16	177.43	257.85	698.44
Simvastatin 10mg (n = 3)	687.64	247.14	461.27	1396.05
Simvastatin 20mg (n = 11)	421.55	130.18	192.94	744.67
Simvastatin 30mg (n = 0) 3 x 10mg	N/A	N/A	N/A	N/A
Simvastatin 40mg (n = 0) 2 x 20mg	N/A	N/A	N/A	N/A
Simvastatin 40mg (n = 7) 1 x 40mg	430.86	124.28	182.06	737.20

Table 3.24, using final drug/dosing regimen as classification, shows annual cost estimates of treatment for secondary prevention patients. Only the group consisting of pravastatin 20mg patients, with a cell size of 47, was large enough for reliable estimates. The total annual estimated direct medical costs for this group was \$585.92, with mean estimated annual drug acquisition costs of \$285.15, mean estimated annual office visits costs of \$124.75, and mean estimated annual lab test costs of \$176.02.

For the other smaller groups, the lowest total estimated annual direct medical costs were \$473.49 for the two simvastatin 5mg patients and the highest were \$1300.26 for the one simvastatin 20mg, twice daily, patients. The mean estimated annual drug acquisition costs ranged from \$238.30 for the two simvastatin 5mg patients to \$971.51 for the single simvastatin 20mg, twice daily, patient. The mean estimated annual office visit costs ranged from \$111.83 for the one pravastatin 60mg (three by 20mg) patient to \$228.12 for the single simvastatin 10mg patient. The mean estimated annual lab costs ranged from \$90.84 for the single simvastatin 20mg patient to \$243.33 for the one atorvastatin 20mg patient.

Table 3.24 Annual Cost Estimates of Treatment - SECONDARY PREVENTION Using FINAL DRUG/DOSING REGIMEN and Mean Costs

DRUG NAME AND DAILY DOSE	DRUG ACQ. COSTS (\$)	OFFICE VISIT COSTS (\$)	LAB TEST COSTS (\$)	TOTAL DIR. MED. COSTS (\$)
Atorvastatin 10mg (n = 0)	N/A	N/A	N/A	N/A
Atorvastatin 20mg (n = 1)	435.65	135.79	243.33	814.77
Atorvastatin 40mg (n = 2)	790.16	122.78	130.40	1043.34
Fluvastatin 20mg (n = 0)	N/A	N/A	N/A	N/A
Fluvastatin 40mg (n = 0)	N/A	N/A	N/A	N/A
Pravastatin 10mg (n = 4) 1 x 10mg	294.74	139.94	148.35	583.003
Pravastatin 20mg (n = 1) 1/2 x 20mg	263.10	126.74	56.78	446.62
Pravastatin 20mg (n = 47)	285.15	124.75	176.02	585.92
Pravastatin 40mg (n = 2) 2 x 20mg	511.00	126.74	138.29	776.03
Pravastatin 40mg (n = 19) 1 x 40mg	524.98	177.85	183.67	886.50
Pravastatin 60mg (n = 1) 3 x 20mg	644.12	111.83	174.48	930.43
Pravastatin 80mg (n = 0) 2 x 40mg	N/A	N/A	N/A	N/A
Simvastatin 5mg (n = 2)	238.30	122.51	112.68	473.49
Simvastatin 10mg (n = 1)	430.70	228.12	136.27	795.09
Simvastatin 20mg (n = 1)	561.86	126.74	90.84	779.44
Simvastatin 30mg (n = 1) 3 x 10mg	308.22	168.98	227.11	704.31
Simvastatin 40mg (n = 1) 2 x 20mg	971.51	158.42	170.33	1300.26
Simvastatin 40mg (n = 8) 1 x 40mg	598.11	138.52	201.61	938.24

FINAL DRUG ALONE AS CLASSIFICATION

Tables 3.25 through 3.27 use final drug alone as the classification and show calculations for the overall sample, the primary prevention group, and the secondary prevention group. Only pravastatin and simvastatin patients as composites had sufficient cell sizes to meet the minimum requirement of 20 subjects per cell as an overall sample and as primary prevention. The total estimated annual direct medical costs for pravastatin were \$708.14 for the overall sample (n = 238), \$724.96 for the primary prevention patients (n = 164), and \$670.86 for the secondary prevention patients (n = 74). The total estimated annual direct medical costs for simvastatin were \$833.35 for the overall sample (n= 38) and \$818.14 for the primary prevention patients (n = 24).

**Table 3.25 Annual Cost Estimates of Treatment - SAMPLE OVERALL
Using FINAL DRUG and Mean Costs**

DRUG NAME	DRUG ACQ. COSTS (\$)	OFFICE VISIT COSTS (\$)	LAB TEST COSTS (\$)	TOTAL DIR. MED. COSTS (\$)
Atorvastatin (n = 5)	552.60	129.05	162.55	844.20
Fluvastatin (n = 8)	290.14	178.91	222.66	691.71
Pravastatin (n = 238)	355.13	156.43	196.58	708.14
Simvastatin (n = 38)	474.72	147.66	210.97	833.35

**Table 3.26 Annual Cost Estimates of Treatment - PRIMARY PREVENTION
Using FINAL DRUG and Mean Costs**

DRUG NAME	DRUG ACQ. COSTS (\$)	OFFICE VISIT COSTS (\$)	LAB TEST COSTS (\$)	TOTAL DIR. MED. COSTS (\$)
Atorvastatin (n = 2)	373.52	131.95	154.31	659.78
Fluvastatin (n = 8)	290.14	178.91	222.66	691.71
Pravastatin (n = 164)	353.87	164.24	206.85	724.96
Simvastatin (n = 24)	437.73	148.99	231.42	818.14

**Table 3.27 Annual Cost Estimates of Treatment - SECONDARY
PREVENTION Using FINAL DRUG and Mean Costs**

DRUG NAME	DRUG ACQ. COSTS (\$)	OFFICE VISIT COSTS (\$)	LAB TEST COSTS (\$)	TOTAL DIR. MED. COSTS (\$)
Atorvastatin (n = 3)	671.99	127.11	168.05	967.15
Fluvastatin (n = 0)	N/A	N/A	N/A	N/A
Pravastatin (n = 74)	357.91	139.11	173.84	670.86
Simvastatin (n = 14)	538.12	145.39	175.91	859.42

COST-EFFECTIVENESS RATIOS

Cost-effectiveness analysis "is an approach used for identifying, measuring, and comparing the significant costs and consequences of alternative interventions."⁶ Cost-effectiveness is expressed in ratio form using monetary value per some natural unit that can be measured. For this study, the effectiveness of the statins was determined by the percent reduction in LDL level (a measurable natural unit). The cost to be used in calculating the cost-effectiveness ratios for the various statin drugs and drug/dosing regimen combination will be the estimated annual total direct medical cost of each. The cost-effectiveness ratios calculated for this study show the cost in estimated annual total direct medical costs required to produce a one percent reduction in LDL level, or price per percent reduction (PPR) in LDL level. For those patients having a negative percent decrease in LDL level (meaning their LDL levels rose over the course of treatment), no cost-effectiveness ratios were calculated (effectiveness must be demonstrated first).

INITIAL DRUG AS CLASSIFICATION - OVERALL SAMPLE

Table 3.28, using initial drug/dosing regimen and mean overall percent reduction in LDL as classifiers, shows calculation of the cost-effectiveness ratios. For the sample overall, only three sub-sets of pravastatin had sufficient cell size (minimum of 20 subjects per cell) for meaningful calculations. Pravastatin 10mg (once daily) had a cost-effectiveness ratio of \$41.45 PPR. Pravastatin 20mg had a cost-effectiveness ratio of \$35.53 PPR. Pravastatin 40mg (once daily) had a cost-effectiveness ratio of \$178.52 PPR.

Table 3.28 Cost-Effectiveness (Annual Treatment Costs/ % Reduction in LDL) - SAMPLE OVERALL - Using INITIAL DRUG/DOSING and MEAN OVERALL % LDL REDUCTION

DRUG NAME AND DAILY DOSE	ESTIMATED MEAN ANNUAL DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin	N/A	N/A	N/A
Fluvastatin 20mg (n = 8)	691.71	9.10%	76.01
Pravastatin 10mg (n = 40) 1 x 10mg	841.75	20.31%	41.45
Pravastatin 10mg (n = 1) 1/2 x 20mg	446.62	9.60%	46.52
Pravastatin 20mg (n = 193)	659.88	18.57%	35.53
Pravastatin 40mg (n = 8) 2 x 20mg	754.67	-9.68%	N/A
Pravastatin 40mg (n = 35) 1 x 40mg	964.02	5.40%	178.52
Simvastatin 10mg (n = 1)	795.09	-70.86%	N/A
Simvastatin 20mg (n = 3)	792.33	35.45%	22.35

Table 3.29 uses initial drug/dosing regimen as the classifier, but uses the difference between baseline and final LDL level on record as the basis for the observed percent decrease in LDL. The cost-effectiveness ratios for the overall sample's three pravastatin groups are \$37.53 PPR for the 10mg patients, \$32.10 PPR for the 20mg patients, and \$215.66 PPR for the 40mg patients.

Table 3.29 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) - SAMPLE OVERALL - Using INITIAL DRUG/DOSING REGIMEN and % LDL REDUCTION BETWEEN BASELINE and LAST RECORDED LDL

DRUG NAME AND DAILY DOSE	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST-EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin	N/A	N/A	N/A
Fluvastatin 20mg (n = 8)	691.71	8.90%	77.72
Pravastatin 10mg (n = 40) 1 x 10mg	841.75	22.43%	37.53
Pravastatin 10mg (n = 1) 1/2 x 20mg	446.62	9.60%	46.52
Pravastatin 20mg (n = 193)	659.88	20.56%	32.10
Pravastatin 40mg (n = 8) 2 x 20mg	754.67	-5.01%	N/A
Pravastatin 40mg (n = 35) 1 x 40mg	964.02	4.47%	215.66
Simvastatin 10mg (n = 1)	795.09	-70.86%	N/A
Simvastatin 20mg (n = 3)	792.33	35.67%	22.21

INITIAL DRUG AS CLASSIFICATION - PRIMARY PREVENTION

Table 3.30 looks strictly at primary prevention patients, using initial drug/dosing regimen and mean overall percent LDL reduction as classifiers. Only pravastatin 10mg (once daily) and pravastatin 20mg meet the cell size of 20 requirement. Their cost-effectiveness ratios were \$41.23 PPR and \$37.76 PPR respectively.

Table 3.30 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) - PRIMARY PREVENTION - Using INITIAL DRUG/DOSING REGIMEN and MEAN OVERALL % LDL REDUCTION

DRUG NAME AND DAILY DOSE	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST-EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin	N/A	N/A	N/A
Fluvastatin 20mg (n = 8)	691.71	9.10%	76.01
Pravastatin 10mg (n = 31) 1 x 10mg	909.05	22.05%	41.23
Pravastatin 10mg (n = 0) 1/2 x 20mg	N/A	N/A	N/A
Pravastatin 20mg (n = 132)	659.96	17.48%	37.76
Pravastatin 40mg (n = 6) 2 x 20mg	663.26	-13.02%	N/A
Pravastatin 40mg (n = 19) 1 x 40mg	1010.07	6.82%	148.10
Simvastatin 10mg (n = 0)	N/A	N/A	N/A
Simvastatin 20mg (n = 2)	691.15	42.87%	16.12

Table 3.31 uses initial drug/dosing regimen as classification, but uses the difference between baseline and last LDL of record to determine the observed percent decrease in LDL in primary prevention patients. Pravastatin 10mg (once daily) had a cost-effectiveness ratio of \$37.78 PPR. Pravastatin 20mg had a cost-effectiveness ratio of \$32.01 PPR.

Table 3.31 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) - PRIMARY PREVENTION - Using INITIAL DRUG/DOSING and % LDL REDUCTION BETWEEN BASELINE and LAST RECORDED LDL

DRUG NAME AND DAILY DOSE	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST-EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin	N/A	N/A	N/A
Fluvastatin 20mg (n = 8)	691.71	8.90%	77.72
Pravastatin 10mg (n = 31) 1 x 10mg	909.05	24.06%	37.78
Pravastatin 10mg (n = 0) 1/2 x 20mg	N/A	N/A	N/A
Pravastatin 20mg (n = 132)	659.96	20.62%	32.01
Pravastatin 40mg (n = 6) 2 x 20mg	663.26	-7.96%	N/A
Pravastatin 40mg (n = 19) 1 x 40mg	1010.07	5.18%	194.99
Simvastatin 10mg (n = 0)	N/A	N/A	N/A
Simvastatin 20mg (n = 2)	691.15	46.27%	14.94

INITIAL DRUG CLASSIFICATION - SECONDARY PREVENTION

Looking at secondary prevention patients on initial drug/dosing regimen and using mean overall percent reduction in LDL as measures of effectiveness, only pravastatin 20mg had sufficient cell size at 61. Table 3.32 shows pravastatin 20mg's cost-effectiveness ratio to be \$31.54 PPR. Table 3.33 uses the difference between baseline and last recorded LDL value to calculate observed percent decrease in LDL in the same patients. Here the cost-effectiveness ratio for pravastatin 20mg is \$32.26 PPR.

Table 3.32 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) - SECONDARY PREVENTION - Using INITIAL DRUG/DOSING REGIMEN and MEAN OVERALL % LDL REDUCTION

DRUG NAME AND DAILY DOSE	ANNUAL DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST-EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin	N/A	N/A	N/A
Fluvastatin	N/A	N/A	N/A
Pravastatin 10mg (n = 9) 1 x 10mg	609.97	14.31%	42.62
Pravastatin 10mg (n = 1) 1/2 x 20mg	446.62	9.60%	46.52
Pravastatin 20mg (n = 61)	659.72	20.92%	31.54
Pravastatin 40mg (n = 2) 2 x 20mg	1028.94	0.35%	2939.83
Pravastatin 40mg (n = 16) 1 x 40mg	909.31	3.71%	245.10
Simvastatin 10mg (n = 1)	795.09	-70.86%	N/A
Simvastatin 20mg (n = 1)	994.70	20.61%	48.26

**Table 3.33 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
SECONDARY PREVENTION - Using INITIAL DRUG/DOSING and %
LDL REDUCTION BETWEEN BASELINE and LAST RECORDED LDL**

DRUG NAME AND DAILY DOSE	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin (n = 0)	N/A	N/A	N/A
Fluvastatin (n = 0)	N/A	N/A	N/A
Pravastatin 10mg (n = 9) 1 x 10mg	609.97	16.83%	36.24
Pravastatin 10mg (n = 1) 1/2 x 20mg	446.62	9.60%	46.52
Pravastatin 20mg (n = 61)	659.72	20.45%	32.26
Pravastatin 40mg (n = 2) 2 x 20mg	1028.94	3.83%	268.65
Pravastatin 40mg (n = 16) 1 x 40mg	909.31	3.63%	250.50
Simvastatin 10mg (n = 1)	795.09	-70.86%	N/A
Simvastatin 20mg (n = 1)	994.70	14.47%	68.74

SUMMARY - INITIAL DRUG

Tables 3.34 through 3.39 show cost-effectiveness ratio calculations for initial drug by each approach to observed mean percent decrease in LDL and by overall sample, primary prevention, and secondary prevention patients. Only pravastatin had sufficient cell size. The calculated cost-effectiveness ratios ranged from \$39.36 PPR for pravastatin primary prevention patients using the baseline to last recorded LDL percent reduction as the measure of observed effectiveness, to a high of \$45.49 PPR for pravastatin primary prevention patients using the mean overall percent LDL reduction.

**Table 3.34 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
SAMPLE OVERALL - Using INITIAL DRUG and MEAN OVERALL %
LDL REDUCTION**

DRUG NAME	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin (n = 0)	N/A	N/A	N/A
Fluvastatin (n = 8)	691.71	9.10%	76.01
Pravastatin (n = 277)	726.54	16.31%	44.55
Simvastatin (n = 4)	793.02	8.87%	89.40

**Table 3.35 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
SAMPLE OVERALL - Using INITIAL DRUG and % LDL REDUCTION
BETWEEN BASELINE and LAST RECORDED LDL**

DRUG NAME	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin (n = 0)	N/A	N/A	N/A
Fluvastatin (n = 8)	691.71	8.90%	77.72
Pravastatin (n = 277)	726.54	18.02%	40.32
Simvastatin (n = 4)	793.02	9.04%	87.72

**Table 3.36 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
PRIMARY PREVENTION - Using INITIAL DRUG and MEAN OVERALL
% LDL REDUCTION**

DRUG NAME	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin (n = 0)	N/A	N/A	N/A
Fluvastatin (n = 8)	691.71	9.10%	76.01
Pravastatin (n = 188)	736.52	16.19%	45.49
Simvastatin (n = 2)	691.15	42.87%	16.13

**Table 3.37 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
PRIMARY PREVENTION - Using INITIAL DRUG and % LDL
REDUCTION BETWEEN BASELINE and LAST RECORDED LDL**

DRUG NAME	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin (n = 0)	N/A	N/A	N/A
Fluvastatin (n = 8)	691.71	8.90%	77.72
Pravastatin (n = 188)	736.52	18.71%	39.36
Simvastatin (n = 2)	691.15	46.27%	14.94

**Table 3.38 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
SECONDARY PREVENTION - Using INITIAL DRUG and MEAN
OVERALL % LDL REDUCTION**

DRUG NAME	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin (n = 0)	N/A	N/A	N/A
Fluvastatin (n = 0)	N/A	N/A	N/A
Pravastatin (n = 277)	705.47	16.57%	42.58
Simvastatin (n = 4)	894.90	-25.12%	N/A

**Table 3.39 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
SECONDARY PREVENTION - Using INITIAL DRUG and % LDL
REDUCTION BETWEEN BASELINE and LAST RECORDED LDL**

DRUG NAME	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin (n = 0)	N/A	N/A	N/A
Fluvastatin (n = 0)	N/A	N/A	N/A
Pravastatin (n = 277)	705.47	16.56%	42.60
Simvastatin (n = 4)	894.90	-28.19%	N/A

FINAL DRUG AS CLASSIFICATION - SAMPLE OVERALL

Cost-effectiveness ratio calculations were performed using final drug or drug/dosing regimen and both types of effectiveness calculations on the overall sample as well as primary prevention and secondary patients. Table 3.40 shows the cost-effectiveness ratio calculations for the overall sample using mean overall percent reduction in LDL. Pravastatin 10mg (once daily) had a cost-effectiveness ratio of \$37.41 PPR. Pravastatin 20mg had a cost-effectiveness ratio of \$33.79 PPR. Pravastatin 40mg (once daily) had a cost-effectiveness ratio of \$77.50 PPR.

For those cells not containing the minimum number of subjects, the cost-effectiveness ratios ranged from \$21.67 PPR for the single atorvastatin 10mg patient to \$2875.31 PPR for the 12 simvastatin 20mg patients. Those cells having a negative observed mean percent decrease in LDL did not have cost-effectiveness ratios calculated as no effectiveness was observed.

**Table 3.40 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
SAMPLE OVERALL - Using FINAL DRUG/DOSING REGIMEN and
MEAN OVERALL % LDL REDUCTION**

DRUG NAME AND DAILY DOSE	ANNUAL DIR. MED. COSTS (\$)	OBSERVED MEAN % Δ IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin 10mg (n = 1)	534.72	24.68%	21.67
Atorvastatin 20mg (n = 2)	799.82	-10.35%	N/A
Atorvastatin 40mg (n = 2)	1043.34	34.34%	30.38
Fluvastatin 20mg (n = 7)	650.49	7.92%	82.13
Fluvastatin 40mg (n = 1)	980.20	17.34%	56.53
Pravastatin 10mg (n = 25) 1 x 10mg	766.09	20.48%	37.41
Pravastatin 10mg (n = 1) 1/2 x 20mg	446.62	9.60%	46.52
Pravastatin 20mg (n = 158)	634.67	18.78%	33.79
Pravastatin 40mg (n = 5) 2 x 20mg	748.25	-8.19%	N/A
Pravastatin 40mg (n = 45) 1 x 40mg	899.76	11.61%	77.50
Pravastatin 60mg (n = 2) 3 x 20mg	1068.42	35.42%	30.16
Pravastatin 80mg (n = 2) 2 x 40mg	1146.92	6.08%	188.64
Simvastatin 5mg (n = 5)	608.46	24.84%	24.50
Simvastatin 10mg (n = 4)	1245.80	-2.56%	N/A
Simvastatin 20mg (n = 12)	747.58	0.26%	2875.31
Simvastatin 30mg (n = 1) 3 x 10mg	704.31	30.31%	23.24
Simvastatin 40mg (n = 1) 2 x 20mg	1300.26	10.63%	122.32
Simvastatin 40mg (n = 15) 1 x 40mg	844.41	17.96%	47.02

Table 3.41, looking at the overall sample, used final drug/dosing regimen as classification and percent LDL reduction between baseline and final recorded LDL. Pravastatin 10mg (once daily) had a cost-effectiveness ratio of \$35.73 PPR. Pravastatin 20mg had a cost-effectiveness ratio of \$31.59 PPR. Pravastatin 40mg had a cost-effectiveness ratio of \$78.58 PPR.

For those dosing regimens having less than 20 subjects per cell, the cost-effectiveness ratios ranged from \$8.54 PPR for one atorvastatin 10mg patient to \$180.14 PPR for the 12 simvastatin 20mg patients. Those cells having a negative observed mean percent decrease in LDL between baseline and last recorded LDL did not have cost-effectiveness ratios calculated as no effectiveness was observed.

**Table 3.41 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
SAMPLE OVERALL - Using FINAL DRUG/DOSING REGIMEN and %
LDL REDUCTION BETWEEN BASELINE and LAST RECORDED LDL**

DRUG NAME AND DAILY DOSE	ANNUAL DIR. MED. COSTS (\$)	OBSERVED MEAN % Δ IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin 10mg (n = 1)	534.72	62.60%	8.54
Atorvastatin 20mg (n = 2)	799.82	-3.16%	N/A
Atorvastatin 40mg (n = 2)	1043.34	37.82%	27.59
Fluvastatin 20mg (n = 7)	650.49	7.12%	91.36
Fluvastatin 40mg (n = 1)	980.20	21.39%	45.83
Pravastatin 10mg (n = 25) 1 x 10mg	766.09	21.44%	35.73
Pravastatin 10mg (n = 1) 1/2 x 20mg	446.62	9.60%	46.52
Pravastatin 20mg (n = 158)	634.67	20.09%	31.59
Pravastatin 40mg (n = 5) 2 x 20mg	748.25	-7.73%	N/A
Pravastatin 40mg (n = 45) 1 x 40mg	899.76	11.45%	78.58
Pravastatin 60mg (n = 2) 3 x 20mg	1068.42	38.00%	28.12
Pravastatin 80mg (n = 2) 2 x 40mg	1146.92	13.52%	84.83
Simvastatin 5mg (n = 5)	608.46	24.83%	24.51
Simvastatin 10mg (n = 4)	1245.80	-4.93%	N/A
Simvastatin 20mg (n = 12)	747.58	4.15%	180.14
Simvastatin 30mg (n = 1) 3 x 10mg	704.31	48.12%	14.64
Simvastatin 40mg (n = 1) 2 x 20mg	1300.26	22.41%	58.02
Simvastatin 40mg (n = 15) 1 x 40mg	844.41	24.83%	34.01

FINAL DRUG AS CLASSIFICATION - PRIMARY PREVENTION

Table 3.42 looked at primary prevention patients, using final drug/dosing regimen and mean overall percent LDL reduction. The cost-effectiveness ratio for pravastatin 10mg was \$36.51 PPR. The cost-effectiveness ratio for pravastatin 20mg was \$36.41 PPR. The cost-effectiveness ratio for pravastatin 40mg was \$74.12 PPR.

For those cells not containing the minimum number of subjects, the cost-effectiveness ratios ranged from \$21.33 PPR for the three simvastatin 5mg patients to \$954.71 PPR for the 11 simvastatin 20mg patients. Those cells having a negative observed mean percent decrease in LDL did not have cost-effectiveness ratios calculated as no effectiveness was observed.

**Table 3.42 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
PRIMARY PREVENTION - Using FINAL DRUG/DOSING REGIMEN
and MEAN OVERALL % LDL REDUCTION**

DRUG NAME AND DAILY DOSE	ANNUAL DIR. MED. COSTS (\$)	OBSERVED MEAN % Δ IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin 10mg (n = 1)	534.72	24.68%	21.67
Atorvastatin 20mg (n = 1)	784.86	29.23%	26.85
Atorvastatin 40mg (n = 0)	N/A	N/A	N/A
Fluvastatin 20mg (n = 7)	650.50	7.92%	82.13
Fluvastatin 40mg (n = 1)	980.20	17.34%	56.53
Pravastatin 10mg (n = 21) 1 x 10mg	800.97	21.94%	36.51
Pravastatin 10mg (n = 0) 1/2 x 20mg	N/A	N/A	N/A
Pravastatin 20mg (n = 111)	655.30	18.00%	36.41
Pravastatin 40mg (n = 3) 2 x 20mg	729.73	-8.33%	N/A
Pravastatin 40mg (n = 26) 1 x 40mg	909.43	12.27%	74.12
Pravastatin 60mg (n = 1) 3 x 20mg	1206.40	20.34%	59.31
Pravastatin 80mg (n = 2) 2 x 40mg	1146.92	6.08%	188.64
Simvastatin 5mg (n = 3)	698.44	32.74%	21.33
Simvastatin 10mg (n = 3)	1396.05	20.21%	69.08
Simvastatin 20mg (n = 11)	744.67	0.78%	954.71
Simvastatin 30mg (n = 0) 3 x 10mg	N/A	N/A	N/A
Simvastatin 40mg (n = 0) 2 x 20mg	N/A	N/A	N/A
Simvastatin 40mg (n = 7) 1 x 40mg	737.20	17.41%	42.34

Table 3.43 looked at the same patients but used the percent LDL reduction between baseline and last recorded LDL level. The cost-effectiveness ratio for pravastatin 10mg was \$34.69 PPR. The cost-effectiveness ratio for pravastatin 20mg was \$32.20 PPR. The cost-effectiveness ratio for pravastatin 40mg was \$59.02 PPR.

For those dosing regimens having less than 20 subjects per cell, the cost-effectiveness ratios ranged from \$8.54 PPR for one atorvastatin 10mg patient to \$202.91 PPR for the 11 simvastatin 20mg patients. Those cells having a negative observed mean percent decrease in LDL between baseline and last recorded LDL did not have cost-effectiveness ratios calculated as no effectiveness was observed.

**Table 3.43 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
PRIMARY PREVENTION - Using FINAL DRUG/DOSING and % LDL
REDUCTION BETWEEN BASELINE and LAST RECORDED LDL**

DRUG NAME AND DAILY DOSE	ANNUAL DIR. MED. COSTS (\$)	OBSERVED MEAN % Δ IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin 10mg (n = 1)	534.72	62.60%	8.54
Atorvastatin 20mg (n = 1)	784.86	33.69%	23.30
Atorvastatin 40mg (n = 0)	N/A	N/A	N/A
Fluvastatin 20mg (n = 7)	650.50	7.12%	91.36
Fluvastatin 40mg (n = 1)	980.20	21.39%	45.82
Pravastatin 10mg (n = 21) 1 x 10mg	800.97	23.09%	34.69
Pravastatin 10mg (n = 0) 1/2 x 20mg	N/A	N/A	N/A
Pravastatin 20mg (n = 111)	655.30	20.35%	32.20
Pravastatin 40mg (n = 3) 2 x 20mg	729.73	-8.97%	N/A
Pravastatin 40mg (n = 26) 1 x 40mg	909.43	15.41%	59.02
Pravastatin 60mg (n = 1) 3 x 20mg	1206.40	14.43%	83.60
Pravastatin 80mg (n = 2) 2 x 40mg	1146.92	13.52%	84.83
Simvastatin 5mg (n = 3)	698.44	30.35%	23.01
Simvastatin 10mg (n = 3)	1396.05	17.05%	81.88
Simvastatin 20mg (n = 11)	744.67	3.67%	202.91
Simvastatin 30mg (n = 0) 3 x 10mg	N/A	N/A	N/A
Simvastatin 40mg (n = 0) 2 x 20mg	N/A	N/A	N/A
Simvastatin 40mg (n = 7) 1 x 40mg	737.20	24.67%	29.88

FINAL DRUG AS CLASSIFICATION - SECONDARY PREVENTION

Table 3.44 looked at secondary prevention patients, using final drug/dosing regimen and mean overall percent LDL reduction. Only the pravastatin 20mg patients had a sufficient cell size at 47. The cost-effectiveness ratio for pravastatin 20mg was \$28.42 PPR.

For those cells not containing the minimum number of subjects, the cost-effectiveness ratios ranged from \$18.42 PPR for the single pravastatin 60mg (three by 20mg) patient to \$122.32 PPR for the one simvastatin 40mg (two by 20mg) patient. Those cells having a negative observed mean percent decrease in LDL did not have cost-effectiveness ratios calculated as no effectiveness was observed.

**Table 3.44 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
SECONDARY PREVENTION - Using FINAL DRUG/DOSING REGIMEN
and MEAN OVERALL % LDL REDUCTION**

DRUG NAME AND DAILY DOSE	ANNUAL DIR. MED. COSTS (\$)	OBSERVED MEAN % Δ IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin 10mg (n = 0)	N/A	N/A	N/A
Atorvastatin 20mg (n = 1)	814.77	-49.94%	N/A
Atorvastatin 40mg (n = 2)	1043.34	34.34%	30.38
Fluvastatin 20mg (n = 0)	N/A	N/A	N/A
Fluvastatin 40mg (n = 0)	N/A	N/A	N/A
Pravastatin 10mg (n = 4) 1 x 10mg	583.03	12.81%	45.51
Pravastatin 10mg (n = 1) 1/2 x 20mg	446.62	9.60%	46.52
Pravastatin 20mg (n = 47)	585.92	20.62%	28.42
Pravastatin 40mg (n = 2) 2 x 20mg	776.03	-7.99%	N/A
Pravastatin 40mg (n = 19) 1 x 40mg	886.50	10.70%	82.85
Pravastatin 60mg (n = 1) 3 x 20mg	930.43	50.51%	18.42
Pravastatin 80mg (n = 0) 2 x 40mg	N/A	N/A	N/A
Simvastatin 5mg (n = 2)	473.49	12.99%	36.45
Simvastatin 10mg (n = 1)	795.09	-70.86%	N/A
Simvastatin 20mg (n = 1)	779.44	-5.56%	N/A
Simvastatin 30mg (n = 1) 3 x 10mg	704.31	30.31%	23.24
Simvastatin 40mg (n = 1) 2 x 20mg	1300.26	10.63%	122.32
Simvastatin 40mg (n = 8) 1 x 40mg	938.24	18.44%	50.88

Table 3.45 looked at the same people but used the percent LDL reduction between baseline and last recorded LDL level as the measure of effectiveness. Pravastatin 20mg patients, the only group with a cell size greater than 20, had a cost-effectiveness ratio of \$30.09 PPR.

For those dosing regimens having less than 20 subjects per cell, the cost-effectiveness ratios ranged from \$14.64 PPR for one simvastatin 30mg (three by 10mg) patient to \$146.77 PPR for the 19 pravastatin 40mg (one by 40mg) patients. Those cells having a negative observed mean percent decrease in LDL between baseline and last recorded LDL did not have cost-effectiveness ratios calculated as no effectiveness was observed.

**Table 3.45 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
SECONDARY PREVENTION - Using FINAL DRUG/DOSING and % LDL
REDUCTION BETWEEN BASELINE and LAST RECORDED LDL**

DRUG NAME AND DAILY DOSE	ANNUAL DIR. MED. COSTS (\$)	OBSERVED MEAN % Δ IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin 10mg (n = 0)	N/A	N/A	N/A
Atorvastatin 20mg (n = 1)	814.77	-40.00%	N/A
Atorvastatin 40mg (n = 2)	1043.34	37.82%	27.59
Fluvastatin 20mg (n = 0)	N/A	N/A	N/A
Fluvastatin 40mg (n = 0)	N/A	N/A	N/A
Pravastatin 10mg (n = 4) 1 x 10mg	583.03	12.81%	45.51
Pravastatin 10mg (n = 1) 1/2 x 20mg	446.62	9.60%	46.52
Pravastatin 20mg (n = 47)	585.92	19.47%	30.09
Pravastatin 40mg (n = 2) 2 x 20mg	776.03	-5.86%	N/A
Pravastatin 40mg (n = 19) 1 x 40mg	886.50	6.04%	146.77
Pravastatin 60mg (n = 1) 3 x 20mg	930.43	61.57%	15.11
Pravastatin 80mg (n = 0) 2 x 40mg	N/A	N/A	N/A
Simvastatin 5mg (n = 2)	473.49	16.32%	29.01
Simvastatin 10mg (n = 1)	795.09	-70.86%	N/A
Simvastatin 20mg (n = 1)	779.44	9.40%	82.92
Simvastatin 30mg (n = 1) 3 x 10mg	704.31	48.12%	14.64
Simvastatin 40mg (n = 1) 2 x 20mg	1300.26	22.41%	58.02
Simvastatin 40mg (n = 8) 1 x 40mg	938.24	24.96%	37.59

FINAL DRUG AS CLASSIFIER - SUMMARY

Tables 3.46 through 3.51 used final prescribed drug as the classifier. Tables 3.46 and Table 3.47 looked at the overall sample with mean overall percent LDL reduction and difference between baseline and final LDL level respectively. The cost-effectiveness ratios for pravastatin patients were \$41.58 PPR (mean change) and \$39.21 PPR (last change), respectively, and \$74.08 PPR (mean change) and \$53.05 PPR (last change) for simvastatin. Table 3.48 and Table 3.49 looked at primary prevention patients using mean overall percent LDL reduction and difference between baseline and last LDL level respectively. The calculated pravastatin cost-effectiveness ratios were \$42.67 PPR (mean change) and \$37.64 PPR (last change), respectively, and \$67.90 (mean change) and \$55.21 PPR (last change) for simvastatin. Table 3.50 and Table 3.51 looked at secondary prevention patients using mean overall percent reduction in LDL and percent change between baseline and final LDL value. The cost-effectiveness ratios for pravastatin 20mg were \$39.16 PPR (mean change) and \$43.53 PPR (last change), respectively. No other cells met the minimum requirement of 20 subjects per cell.

**Table 3.46 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
SAMPLE OVERALL - Using FINAL DRUG and MEAN OVERALL %
LDL REDUCTION**

DRUG NAME	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin (n = 5)	844.20	14.53%	58.10
Fluvastatin (n = 8)	691.71	9.10%	76.01
Pravastatin (n = 238)	708.14	17.03%	41.58
Simvastatin (n = 38)	833.35	11.25%	74.08

**Table 3.47 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
SAMPLE OVERALL - Using FINAL DRUG and % LDL REDUCTION
BETWEEN BASELINE and LAST RECORDED LDL**

DRUG NAME	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin (n = 5)	844.20	26.38%	32.00
Fluvastatin (n = 8)	691.71	8.90%	77.72
Pravastatin (n = 238)	708.14	18.06%	39.21
Simvastatin (n = 38)	833.35	15.71%	53.05

**Table 3.48 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
PRIMARY PREVENTION - Using FINAL DRUG and MEAN OVERALL
% LDL REDUCTION**

DRUG NAME	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin (n = 2)	659.78	26.95%	24.48
Fluvastatin (n = 8)	691.71	9.10%	76.01
Pravastatin (n = 164)	724.96	16.99%	42.67
Simvastatin (n = 24)	818.14	12.05%	67.90

**Table 3.49 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
PRIMARY PREVENTION - Using FINAL DRUG and % LDL
REDUCTION BETWEEN BASELINE and LAST RECORDED LDL**

DRUG NAME	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin (n = 2)	659.78	48.14%	13.71
Fluvastatin (n = 8)	691.71	8.90%	77.72
Pravastatin (n = 164)	724.96	19.26%	37.64
Simvastatin (n = 24)	818.14	14.82%	55.21

**Table 3.50 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
SECONDARY PREVENTION - Using FINAL DRUG and MEAN
OVERALL % LDL REDUCTION**

DRUG NAME	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin (n = 3)	967.15	6.25%	154.74
Fluvastatin (n = 0)	N/A	N/A	N/A
Pravastatin (n = 74)	670.86	17.13%	39.16
Simvastatin (n = 14)	859.42	9.86%	87.16

**Table 3.51 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
SECONDARY PREVENTION - Using FINAL DRUG and % LDL
REDUCTION BETWEEN BASELINE and LAST RECORDED LDL**

DRUG NAME	ESTIMATED ANNUAL MEAN DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
Atorvastatin (n = 3)	1141.80	11.88%	96.11
Fluvastatin (n = 0)	N/A	N/A	N/A
Pravastatin (n = 74)	670.86	15.41%	43.53
Simvastatin (n = 14)	859.42	17.24%	49.85

SENSITIVITY ANALYSES

Lab test costs and provider office visit costs were varied by $\pm 20\%$ to see how this impacted the cost-effectiveness ratios. Only patients receiving pravastatin as the final drug (as a composite with $n = 238$) and patients receiving simvastatin as the final drug (as a composite with $n = 38$) were examined. A composite effectiveness measure of the average of the mean overall percent reduction in LDL and the percent changed between baseline and last recorded LDL was used.

Table 3.52 shows the calculated cost-effectiveness ratios when annual estimated costs for lab tests and provider office visits were varied for pravastatin ($n = 238$) as the final drug prescribed. The values calculated with $\pm 20\%$ cost differences in the mean annual estimated lab test and provider visit costs ranged from \$36.35 PPR to \$44.40 PPR.

Table 3.53 shows the calculated cost-effectiveness ratios when annual estimated costs for lab tests and provider office visits were varied for simvastatin ($n = 38$) as the final drug prescribed. The values calculated with $\pm 20\%$ changes in mean annual estimated non-drug costs ranged from \$56.50 PPR to \$67.14 PPR.

This sensitivity analysis shows that even with varying the non-drug costs by $\pm 20\%$, pravastatin as the final prescribed drug patients demonstrated more favorable cost-effectiveness ratios (dollars per percent reduction in LDL) than simvastatin as the final prescribed drug patients.

**Table 3.52 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
PRAVASTATIN (N = 238) AS FINAL DRUG**

CHANGES	ESTIMATED MEAN ANNUAL DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
High Labs High Visits	778.74	17.54%	44.40
Low Labs Low Visits	637.54	17.54%	36.35
High Labs Low Visits	700.11	17.54%	39.92
Low Labs High Visits	716.17	17.54%	40.83

**Table 3.53 Cost-Effectiveness (Annual Treatment Costs/ % Reduc. in LDL) -
SIMVASTATIN (N = 38) AS FINAL DRUG**

CHANGES	ESTIMATED MEAN ANNUAL DIRECT MEDICAL COSTS (\$)	OBSERVED MEAN % DECREASE IN LDL	COST- EFFECTIVENESS RATIO (\$/PPR)
High Labs High Visits	905.08	13.48%	67.14
Low Labs Low Visits	761.63	13.48%	56.50
High Labs Low Visits	820.69	13.48%	60.88
Low Labs High Visits	846.02	13.48%	62.76

SUMMARY

In summary, this chapter has presented the findings of the study, both as tables and in the text. The selection process of the final study subjects was described in detail and certain patient demographics comparing the original and final subjects were given. Each objective was reported on in detail. Objective one was inconclusive except for certain pravastatin sub-groupings. Objective two was inconclusive except that there were no statistically significant differences detected between the pravastatin and simvastatin patients, the only groups with a cell size greater than 20. Objective three was accomplished for most drug and drug/dosing regimens, although with a cell size of less than 20 for the majority of the groups casts doubt on the practical value of some of the calculated cost-effectiveness ratios.

REFERENCES

1. Pharmacoeconomic Center., PEC Update. 16 October 1995; 96(01):1-A19.
2. Vincent Maher, et al., Primary Prevention of Coronary Heart Disease: What Has WOSCOPS Told Us and What Questions Remain? *Drugs* 1997; 54(1):1-8.
3. Sheldon X. Kong, et al., Efficacy of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors in the Treatment of Patients with Hypercholesterolemia: A Meta-Analysis of Clinical Trials. *Clinical Therapeutics* 1997; 19(4):778-797.
4. D. Hilleman, et al., Pharmacoeconomic Assessment of HMG-CoA Reductase Inhibitor Therapy: An Analysis Based on the CURVES Study. (Poster presentation at ISPOR Lipid Conference in Orlando, FL; November 4-6, 1997).
5. D. M. Huse, et al., Cost-Effectiveness of HMG-CoA Reductase Inhibition in Primary Prevention of CHD: New Evidence Comparing All Available Agents. (Poster presentation at ISPOR Lipid Conference in Orlando, FL; November 4-6, 1997).
6. Elizabeth A. Chrischilles, Chapter 5: Cost-Effectiveness Analysis. Principles of Pharmacoeconomics, Second Edition. J. L. Bootman, R. J. Townsend, and W. F. McGhan. Harvey Whitney Books, Co. Cincinnati, Ohio. c1996. p.77-100.

CHAPTER FOUR

DISCUSSION AND CONCLUSIONS

The purpose of this study was to examine patient outcomes, using LDL cholesterol blood levels as surrogates for long-term cardiovascular effects. The study subjects were selected from all statin users in the military beneficiary population served by the Composite Health Care System (CHCS) computer system in the greater San Antonio area.

The specific objectives of the study were:

1. to determine whether LDL cholesterol blood levels were being lowered by statin therapy in the actual-use setting of military beneficiaries in the San Antonio CHCS population as predicted by the October 1995 Department of Defense (DoD) Pharmacoeconomic Center (PEC) and clinical trials;
2. to determine whether there were any differences in this population in percent LDL reduction between the specific statin drugs used; and
3. to compare the cost-effectiveness by calculating treatment cost (medication costs, office visit costs, and laboratory costs) per percent reduction in LDL cholesterol.

The hypotheses were: (1) there would be no differences between predicted percent LDL reduction and what was observed in the study; (2) there would be no differences between the five currently-marketed statins in the mean

percent reduction in LDL; and (3) there would be no differences in the cost-effectiveness of the five statins.

OVERVIEW

Those eligible for care at military treatment facilities (MTFs) are active duty military members or family members, military retirees or family members, and certain foreign military members and their families while assigned to American military facilities. Retirees are treated at MTFs on a space-available basis and are prioritized as following active duty members, active duty family members, retirees who are members of TRICARE (the military's HMO (health maintenance organization)), retiree family members who are TRICARE members, non-TRICARE retirees, and non-TRICARE retiree family members. Those patients who are Medicare-eligible (over 65 years of age) are no longer eligible for TRICARE membership.

Those who were not selected as final study subjects tended to be older than those who were selected (mean age of 65.34 years \pm 10.28, with a range of 4 to 93, for those not selected vs. mean age of 62.81 years \pm 10.73, with a range of 20 to 85). Those who were not selected tended to have other insurance (including Medicare) than those selected (2694/3495 reporting insurance or 77.1% for those not selected vs. 154/229 reporting insurance or 67.2% for those selected). Those who were selected tended to be TRICARE members more than those not selected (17/229 or 7.4% for those selected vs. 223/3495 or 6.4% for those not selected). The final study subjects (by being younger, having less outside insurance, and

being TRICARE members more frequently), had an increased probability that the MTF served as their primary source of healthcare (through increased access and less incentive to use outside sources). Having an out-of-state address as home of record did not appear to be a major determinant of whether the patient met the selection criteria or not (4052/4121 or 97.7% were Texas residents in the group not selected vs. 285/289 or 98.6% for those who were selected).

Patient gender differed between those who met the selection criteria and those who did not. Those not meeting the selection criteria were more evenly balanced between males and females (2429/4142 or 58.6% male and 1713/4142 or 41.3% female, with five subjects not reporting gender) than those who did meet the selection criteria (190/289 or 65.7% male and 99/289 or 34.3% female). This is not surprising as the risk of coronary heart disease (CHD) begins at age 45 for men but not until 55 years of age or menopause, as discussed Chapter Two. As this study focused on new statin-users, those individuals who were younger and male were at higher risk and more likely to be screened for lipid disorders and subsequently treated. In the actual-use setting of this study, increased access to the MTFs is usually seen in this population as well (129/2599 males or 5.0% were active duty vs. 8/1790 females or 0.4% and 2440/2599 males or 93.9% were military retirees vs. 36/1790 females or 2.0%). As described in Chapter One, most clinical trials have focused on males, which might also have influenced medical practice concerning statin therapy.

When ethnicity between those selected and those not selected was dichotomized as either white or non-white, both groups were similar (81.7% white and 18.3% non-white for those not selected vs. 84.7% white and 15.3%

non-white for those who were selected). Missing values were a problem with this variable as 1964/4147 (or 47.4%) of the non-selected subjects did not report ethnicity as did 99/289 (or 34.3%) of the selected subjects. For the non-selected patients, 13/2183 (or 0.3%) reported being Asian, 91/2183 (or 2.2%) reported being Hispanic, 125/2183 (or 3.0%) reported being other, 170/2183 (or 4.1%) reported being Black, and 1784/2183 (or 43.0%) reported being white. For those who were selected, 3/190 (or 1.0%) reported being Hispanic, 7/190 (or 2.4%) reported being other, 19/190 (or 6.6%) reported being Black, and 1611/190 (or 55.7%) reported being White. Because of the large number of missing values, it is not possible to draw conclusions based on ethnicity sub-groupings.

Because of the disproportionate amount of pravastatin patients in the study population, it was difficult to draw conclusions on statin patients other than pravastatin simply due to small cell size. For objective one, 95 percent confidence intervals (± 1.96 times the standard error of the mean) about the observed mean percent reduction in LDL were created to see if the predicted value fell within the interval. For objective two, head-to-head statin comparisons were not possible due to small cell sizes, with the exception of some simvastatin to pravastatin comparisons in the final prescribed drug category. For objective three, cost-effectiveness ratios could be calculated on all drug or drug/dosing regimens that had positive observed percent reduction in LDL, although small cell sizes lead to the questionable value of some of these calculations.

In randomized controlled clinical trials, patients are assigned to a specific treatment, which they would remain on for the duration of the study. Of the final 289 study subjects, 77.2 percent (223/289) remained on the same drug from start

to finish. A total of 58.5 percent (169/289) remained on the same drug and dose the entire time.

As described in Chapter One, the literature uses a compliance rate of at least 80 percent to consider a patient as having been compliant for the purposes of the study. In the present study, compliance was measured by dividing the number of days of medication received during the study period by the number of days (expressed as months) between initial statin prescription and final fill. For the composite group of 289 final subjects, the mean was 100.00 percent compliance, with a standard deviation of 43.78. For the purposes of this study, 100 percent compliance was achieved by those subjects who received the appropriate amount of medication for the time interval between the initial and final statin fill (such as 180 tablets between January 1 and July 1 of the same year). Only 39 of the 289 final subjects (13.5%) had a compliance rate of less than 80 percent. Individuals who had a compliance rate of over 100 percent were usually involved in multiple drug/dosing regimen changes or were leaving the area for an extended period of time. The military has a policy of allowing up to a 90-day supply of maintenance medications, so if a patient were switched to another drug and/or dosing schedule part-way into the 90-day interval, this would register as excess medication and would inflate the calculated compliance rate. Also, as refill history was used as a surrogate for actual medication usage, there may have been discrepancies between what was actually taken and what appeared to have been taken by the patient.

This study took place in the actual-use environment of outpatient care where patients came not only from around the state of Texas for care (such as

Houston, Dallas, Lubbock, Abilene, and Wichita Falls) but also from out of state on occasion. The sample population tended to be older and many had Medicare or some other form of medical insurance beyond just that provided by the military. From the preliminary analysis of 599 potential subjects, 27 percent had no labs or only one lab on file in CHCS. Distant home locations and the fact that Medicare covers lab work but not prescription medications may have contributed to the relatively low availability of sufficient labs for the purpose of this study. Thus, the appropriate lab work may have been performed but the records maintained outside of the CHCS system and were, therefore, unavailable to this researcher.

Following the PEC guidelines with respect to scheduling of LDL labs did not seem to be common practice in the CHCS provider population. Of the 289 final subjects, 177 (61.2%) had LDL levels at two months after initial statin fill, 141 (48.8%) at the four-month point, and 106 (36.7%) at six months. Of the 289 final subjects, 86 (29.8%) had LDL values available at the nine-months milestone. At the twelve-months point, 74 (25.6%) patients had LDL levels recorded. At 15 and 18 months, only 36 (12.5%) and 10 (3.5%) patients, respectively, had LDL values available. In the final study subjects, only one (0.3%) subject had LDL values beyond 18 months available.

The baseline LDL level was 148.92 mg/dl, with a standard deviation of ± 38.77 , for the composite of all 289 final study subjects. The mean LDL value from baseline to final recorded LDL was 120.73 mg/dl, with a standard deviation of ± 31.91 . The mean final LDL recorded was 117.82, with a standard deviation of ± 34.53 . The mean overall percent reduction in LDL was 16.01 percent, with a

standard deviation of ± 26.12 . The mean percent reduction between baseline and last LDL recorded was 17.64 percent, with a standard deviation of ± 28.75 . In clinical trials, patients must meet very stringent selection criteria, including specific admission LDL levels (such as >130 mg/dl or 3.4 mmol/L but <190 mg/dl or 4.9 mmol/L). Other than the requirement that the patient had at least one pre- and one post-treatment non-zero LDL value on file, no exclusions were made on the basis of admission LDL level.

In clinical trials, patients have a specific schedule for follow up and are encouraged to keep appointments. This is not the case in military treatment facilities (MTFs) where the current environment of down-sizing discourages office visits and provider contact. Especially for the older retirees who are eligible for Medicare coverage, the military is no longer supporting the cradle-to-grave medical benefits that many have come to take for granted over the past 40 years since World War II. Many barriers to access have been implemented in recent years which make it nearly impossible for older retirees to receive much medical care at the MTF beyond having prescriptions filled. This may also account for the low percentage of patients available for final study inclusion (15.4% estimated). In fact, the study subjects tended to be younger than the original sample overall. This might be due to the selection criteria of being statin-naïve, which may have favored younger subjects just being recognized with coronary risk factors.

LIMITATIONS OF THE STUDY

This study was a longitudinal retrospective analysis of an existing database in the non-randomized, multiple group, pretest-posttest format. As such, there is the potential for selection bias in study subjects (not every military beneficiary in the DoD had an equal chance to be included in the study, only those in the greater San Antonio, Texas, area). Also, only those individuals receiving new statin prescriptions in the months of October 1996, April 1997, and October 97 were initially identified as potential study subjects.

The selection criteria for study inclusion were relatively lenient, requiring only that the patient be statin free for six months prior to the initiation of statin therapy, have at least one non-zero LDL value pre- and post-treatment on file, and that more than a single fill of statins was recorded. This allowed for a lot of variability among final study subjects and decreased internal validity. Comorbid conditions were allowed which may also have affected internal consistency of the study.

Costs were based on either 1998 MTF costs or published values. Discounting was not performed as patients did not all start at the same time, ranging August 1996 through October 1997 for the initial statin fill. All prices were calculated using the same rate. The point of view for cost of treatment and benefits from percent reduction in LDL was that of the MTF. Although it is currently becoming more difficult for the older retirees as well as all individual who are Medicare-eligible to be treated at the MTF, they still remain the responsibility of the MTF. Long-term cost-savings (such as only prescribing

statins for the highest at-risk patients vs. everyone who might benefit from statin therapy) or future resource usage (such as additional healthcare costs due to patients living longer as a result of statin therapy preventing fatal heart attacks) were not addressed by this study.

Numerous missing or incomplete lab values denied access to a lot of potentially useful information. There is no way of knowing whether these individuals had similar responses to the statins as was observed in the final study subjects. Because only about 15 percent of the original sample would have been eligible for final subject status, the study subjects may not be representative of the overall statin user population.

One of the major limitations of this study is that there was a lack of sufficient subjects receiving statins other than pravastatin and, to a certain extent, simvastatin. If the cell sizes had been larger for the non-pravastatin groups, more meaningful comparisons between the various statins and/or dosing regimens within the same statin could have been made. From a formulary decision-making perspective, both cost and effectiveness must be factored into the model. Lack of sufficiently large cells for the statins other than pravastatin, as found in this study, makes generalizability beyond the final study subjects difficult.

OBJECTIVE ONE

Objective one was to compare predicted mean percent reduction in LDL with observed mean percent LDL reduction in the final study subjects. With only pravastatin 10mg (once daily), pravastatin 20mg, and pravastatin 40mg (once

daily) having sufficient cell sizes using initial drug/dosing regimen as the classifier and adding simvastatin 40mg (once daily) using classification by final drug/dosing, it was difficult to say much about comparisons between other statin drug/dosing regimens.

Objective one could only be accurately assessed as initial and final drug/dosing regimens for pravastatin 10mg (once daily), pravastatin 20mg, pravastatin 40mg (once daily), and for simvastatin 40mg (once daily) when it was the final drug/dosing regimen used, due to cell size. Pravastatin 10mg and 20mg patients either attained the predicted mean percent LDL reduction level or came very close through the use of 95 percent confidence intervals. Pravastatin 40mg (once daily) and simvastatin 40mg (once daily) failed to attain the predicted values.

Even with pravastatin 40mg's sufficiently large cell size, it is difficult to say why the observed mean percent LDL reductions were so much lower than the predicted value of 33.7 percent ($4.47\% \pm 14.41$ for the overall sample of initial patients and $13.10\% \pm 9.75$ for final overall sample patients). Because the MTFs use a formulary system, with pravastatin as the statin of choice, the lowest dosage of an agent is recommended for initial therapy. It may be that the pravastatin 40mg patients were the more difficult patients who had failed on previous therapy with other non-statin medications.

Atorvastatin is the newest agent to be released, having been on the market only since about July of 1997. It is being touted for triglyceride lowering effects, but the proportion of study patients on the drug was too small to say much about the effects on LDL cholesterol. Since atorvastatin is a non-formulary or "special

request" item, only those individuals having failed on other therapies are likely to receive this medication. Perhaps more dramatic effects would have been seen if the patients could have been followed for the full two and one-half years recommended by the literature to see the full effects of statin therapy in secondary prevention patients.

Another possible explanation for not achieving predicted mean percent LDL reduction could be the presence of underlying conditions or previous therapy with other lipid-lowering agents. Of the 289 final study subjects, 69 (23.9%) received diabetic medications and 44 (15.2%) received thyroid medications, commonly accepted surrogates for these two underlying disease states. Cigarette smoking status is another commonly accepted risk factor for coronary heart disease (CHD), but smoking cessation products tend to be non-formulary at MTFs. Only three (1.0%) of the final study subjects had nicotine patches in their prescription history. When hypertension is classified as receiving anti-hypertensive agents such as hydrochlorothiazide or similar diuretics, 44 (15.2%) of the study patients could be so classified. Other drugs used in the treatment of hypertension, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers, and beta blockers, are also used in the treatment of a variety of other disease states, including migraine headaches, so were not assumed to indicate presence of hypertension, a commonly recognized risk factor for CHD. There were 124 (42.9%) patients receiving ACE inhibitors, 50 (17.3%) receiving calcium channel blockers, and 114 (39.4%) receiving beta blockers. Of the final 289 subjects, 95 had received some type of prior non-statin lipid-lowering therapy. Drugs included niacin, colestipol, cholestyramine, and gemfibrozil.

High-density lipoprotein (HDL) cholesterol levels can represent either a positive or negative risk factor. Positive (at increased risk of CHD) risk factors with respect to pre-treatment mean HDL levels (below 35 mg/dl or 0.9 mmol/L) were seen in 78 (27.0%) patients. Negative (at decreased risk of CHD) risk factors with respect to mean pre-treatment HDL levels (at or above 60 mg/dl or 1.6 mmol/L) were seen in 34 (11.8%) patients.

OBJECTIVE TWO

In objective two, the question of therapeutic differences between the statins was investigated. Again, small and unequal cell sizes made comparisons difficult. Looking at the first statin the patients received, 2.8 percent were on fluvastatin, 95.8 percent were on pravastatin, and 1.4 percent were on simvastatin. Looking at the drug the patient ultimately received, 1.7 percent got atorvastatin, 2.8 percent got fluvastatin, 82.4 percent got pravastatin, and 13.1 percent got simvastatin. The trend towards prescribing simvastatin more frequently (38 at end of study vs. four at the beginning) seems somewhat disturbing from the perspective that while the predicted mean percent reduction in LDL was 35.28 percent, the observed values were 11.25 percent ± 7.84 (mean change) and 15.71 percent ± 8.51 (last change). Looking at mean baseline LDL values between the final prescribed statins, pravastatin patients' mean was 147.58 mg/dl ± 4.92 for 238 patients, simvastatin patients' mean was 151.12 mg/dl ± 12.70 for 38 patients, fluvastatin patients' mean was 179.44 mg/dl ± 13.19 for eight patients, and atorvastatin patients' mean was 147.40 mg/dl ± 36.53 for five patients.

When paired samples *t* tests were run comparing the final pravastatin and simvastatin patients' mean overall percent LDL reduction and percent LDL reduction between baseline and last recorded LDL, pravastatin usage patients tended to have higher mean percent reductions in LDL (mean of 17.03% \pm 3.29 pravastatin vs. 11.25% \pm 8.82 simvastatin) and reductions in LDL between baseline and final LDL (18.06% \pm 3.66 pravastatin vs. 15.711% \pm 9.35 simvastatin) than was seen in simvastatin patients. These differences were not significant at $p = 0.235$ and $p = 0.649$ respectively, not assuming equal variances.

In summary, the questions raised by objective two could not be definitively answered except to say that pravastatin and simvastatin differed in observed mean percent reduction in LDL.

OBJECTIVE THREE

Objective three investigated the cost-effectiveness of the various statin drug/dosing regimens. A cost-effectiveness ratio, expressing annual estimated cost of treatment per one percent mean reduction in LDL level, was calculated for every regimen having a positive observed mean percent reduction in LDL. Whether these cost-effectiveness ratios should be used in future policy making decisions is debatable for those regimens having cell sizes smaller than 20. All values were reported, leaving decisions about the practicality of reported values to the discretion of the reader.

Calculation of estimated total direct medical costs did not include cost of side effect treatment as the most common therapy for statin side effects is

discontinuation of the statin. A few pharmacy comments in the prescription records of the original sample of 4436 included statements about lovastatin or pravastatin causing a rash, but there were no corresponding prescriptions for diphenhydramine capsules or hydrocortisone creams for treatment of this. Costs for other related healthcare expenses could not be adequately identified from the database being used and were not calculated nor incorporated into the annual cost estimate.

When looking at the initial drug prescribed and assuming a cell size of 20, pravastatin 20mg (once daily) was more cost-effective at \$35.53 PPR (mean change) and \$32.10 PPR (last change) than pravastatin 10mg (once daily) at \$41.45 PPR (mean change) and \$37.53 PPR (last change) which was more cost-effective than pravastatin 40mg (once daily) at \$178.52 PPR (mean change) and \$215.66 PPR (last change). Factors other than cost-effectiveness influence provider prescribing habits, although patients with special needs may be started on the lowest dose and then titrated up to maximum or desired effect. Patients on those dosing regimens with higher cost may benefit from additional drug therapy from other lipid-lowering agents instead of just increasing the dosage of the present statin.

When looking at the final drug the patient received prior to the last LDL on record and using only those with a cell size of more than 20, pravastatin 20mg was more cost-effective at \$33.79 PPR (mean change) and \$31.59 PPR (mean change) than pravastatin 10mg (once daily) at \$37.41 PPR (mean change) and \$35.73 PPR (last change) which was more cost-effective than pravastatin 40mg (once daily) at \$77.50 PPR (mean change) and \$78.58 PPR (last change). When

the final drug received during the study period as a composite was the only classification, pravastatin (n = 238) at \$41.58 PPR (mean change) and \$39.21 PPR (last change) was more cost-effective than simvastatin (n = 38) at \$74.08 PPR (mean change) and \$53.05 PPR (last change).

In light of the above relative cost-effectiveness ratios reported for these statin patients, it is surprising that simvastatin use is on the rise but had the highest cost per one percent reduction in LDL in the two groups with sufficient cell sizes. Cost-effectiveness implies value for money spent, or getting the "biggest bang for the buck." Here pravastatin patients demonstrated better cost-effective ratios than simvastatin patients. From the PEC guidelines, pravastatin 10mg is considered interchangeable with simvastatin 5mg and fluvastatin 20mg. Pravastatin 20mg is considered interchangeable with simvastatin 10mg and fluvastatin 40mg. Pravastatin 40mg is considered interchangeable with simvastatin 20mg. Atorvastatin was not available when the guidelines were published and is not addressed here.

From the literature, several studies found fluvastatin to be the most cost-effective statin.^{1,2} In this study, cell sizes were too small to make statistical comparisons for fluvastatin. Direct observation showed that the six final fluvastatin patients had mean annual estimated total direct medical costs of \$1247.44, but an effectiveness of only 6.79 percent reduction in LDL. No conclusions can be drawn about the cost-effectiveness of fluvastatin from this study. Because the fluvastatin patients had the highest baseline LDL levels of all the groups ($179.44 \text{ mg/dl} \pm 13.19$), it is possible that this was the only cardiac risk factor found in these individuals, so the "cheaper" drug would help in the long-

run as opposed to dramatically reducing LDL levels immediately in higher risk patients.

In summary, objective three was achieved for all broad drug categories and for the majority of the dosing regimens. Small cell size makes generalizability outside the scope of this study questionable.

SENSITIVITY ANALYSIS

When the non-drug costs were varied ± 20 percent for final pravastatin and simvastatin users, pravastatin patients demonstrated better cost-effectiveness ratios at \$36.35 PPR to \$44.40 PPR than simvastatin patients at \$56.50 PPR to \$67.14 PPR. This indicates that either drug acquisition costs represent the majority of annual estimated total direct medical costs or that effectiveness as measured by mean percent reduction in LDL influences cost-effectiveness more than annual treatment costs do. In this study, it appears both of the above statements were supported because pravastatin patients had lower estimated treatment costs than simvastatin patients and came closer to the predicted values for percent LDL reduction. This would be a case of getting more effect (greater observed decreases in LDL level) for less money (lower annual estimated treatment costs).

COMPOSITE HEALTH CARE SYSTEM (CHCS)

The CHCS computer system is marketed as being an integrated database system. In reality this is not completely true. While pharmacy, laboratory, and

patient administration files physically reside within the same computer system, they still must be pulled up using separate screens. There are very few relational queries that are possible in real time. The system is still designed towards running reports and then analyzing the printed findings.

Data collection was hampered by having to determine initial statin fill dates and statin-free status prior to making any meaningful lab data collection (it is hard to collect pre- and post-treatment LDL values without knowing start time). Although this may be a problem common to all databases, a more user-friendly data retrieval process in CHCS would be appreciated. Prescription history is displayed ten records at a time; specific prescriptions must be tagged and then itemized for expansion of dispensing history, and then each prescription must be viewed to determine fill dates, quantities dispensed, and time intervals. There is no option that allows viewing a specific type of drug for a specific patient unless the fill dates are already known. Drug utilization reports (DURs) can identify specific patients by specific drugs, but do not include fill dates and are requested based on dispensing location.

The PEC is establishing a more complete prescription database that is more user friendly. Information can be extracted and used in spreadsheets for analysis. The data will be captured from MTFs world-wide and then transferred into this database, so timeliness and completeness are issues here. Using this database, information was extracted for fiscal year 1997 (FY97) for the time period of October 1, 1996, through September 30, 1997. This showed that the original sample of 4436 patients received 25,743 statin prescriptions during this period. Of these prescriptions 514 (2.0%) were for fluvastatin, 134 (0.5%) were

for lovastatin, 24,436 (94.9%) were for pravastatin, and 659 (2.6%) were for simvastatin. Atorvastatin was not available during this time period. A variety of providers wrote these 25,000+ prescriptions, with 33.9 percent being written by staff military physicians, 23.6 percent being written by "outside" physicians (usually civilian physicians), and the remainder being written by an assortment of personnel including medicine, family practice, endocrinology, and cardiology specialists. No lab information and limited patient demographics are currently available in this separate database.

OTHER COMMENTS

Although not a specific objective of this study, when patients were categorized into primary prevention with less than two risk factors, primary prevention with two or more risk factors, or into secondary prevention as described in Chapter Two, 107/289 (or 37.0%) had less than two risk factors, 91/289 (or 31.5%) had two or more risk factors, and 91/289 (or 34.5%) remained secondary prevention patients. This is a very crude categorization using gender, age, smoking status, diuretic usage, presence of diabetes mellitus, and mean baseline HDL levels. When these categories of patients are compared with the NCEP treatment goals (described in Chapter Two), 194/289 (or 67.1%) of all patients reached their respective treatment goals.

Small cell sizes made comparisons of the various statins at each model milestone impractical. Pravastatin and simvastatin final patients were compared at two-months (143 vs. 22 subjects), four-months (115 vs. 22), six-months (711

vs. 29), and nine-months (63 vs. 21). The only significant difference ($p = 0.002$) was at the two-month point, with pravastatin patients having a lower mean LDL (117.21 mg/dl \pm 32.49) than simvastatin patients (139.36 mg/dl \pm 27.34). No other cells were sufficiently large to make any reasonable comparisons.

SUGGESTIONS FOR FURTHER STUDY

Prospective tracking of new statin patients would facilitate data collection and insure that lab values could be more readily available. Since the PEC guidelines are not apparently being followed, new guidelines should be established that reflect current practices better or the published guidelines should be enforced more stringently.

Prospective tracking of specific sub-groups of patients in each of the statin dosing regimens should allow for more meaningful between-statin comparisons with sufficient cell size for statistical analysis.

Tracking cost-effectiveness ratios in response to competitive pricing strategies from year to year would be informative. In the military system, prices are bid yearly, so what is cheapest this year may not be cheapest next year. Cost-effectiveness ratios compensate for this by only focusing on price per outcome. If drug A increases the price by 50% but is still 75% more effective than drug B, drug A may still be more cost-effective even after the price increase.

CONCLUSION

Pravastatin achieves or nearly achieves predicted percent LDL reductions in most cases, with the 10mg and 20mg patients doing better than the 40mg patients. Small cell sizes for the other dosing regimens preclude meaningful interpretation of the findings for these groups.

Pravastatin patients demonstrated a mean cost-effectiveness ratio of \$42.44 PPR as the initial therapy (n = 277) and \$40.40 PPR as the final therapy (n = 238), using annual estimated cost of treatment per one percent decrease in LDL. Simvastatin as the final therapy patients (n = 38) had a mean cost-effectiveness ratio of \$63.56 PPR. Cost-effectiveness ratios were calculated for all other drug/dosing regimens, but small cell sizes limit their usefulness.

In the 1995 PEC guidelines, it was estimated that nearly 500,000 of the six million military beneficiaries over the age of 20 had established CHD. An additional 2.2 million were estimated to have two or more of the recognized positive risk factors present for CHD. The remaining population could have no or only one risk factor present. Although only an estimated 15.4 percent of the original sample would have met all the selection criteria, the 289 final study subjects represent nearly \$1.2 million in estimated annual total direct medical costs, strictly for lipid-lowering therapy with statin drugs.

REFERENCES

1. Marshall E. Spearman, et al., Cost-Effectiveness of Initial Therapy with 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors to Treat Hypercholesterolemia in a Primary Care Setting of a Managed-Care Organization. *Clinical Therapeutics* 1997; 19(3):582-602.
2. Donald Black, et al., Cost Effectiveness of Treatment to National Cholesterol Education Panel (NCEP) Targets with HMG-CoA Reductase Inhibitors: Trial Design. *Pharmacoeconomics* 1997; 12 (2 Pt 2):278-285.

BIBLIOGRAPHY

- Alfred W. Alberts, Discovery, Biochemistry and Biology of Lovastatin. *American Journal of Cardiology* 1988; 62:10J-15J.
- American Heart Association. Atherosclerosis: A Major Cause of Cardiovascular Disease. <http://www.reg.uci.edu/UCI/CARDIOLOGY/PREVENTIVE/FACTS/athero.html>, January 1998..
- Todd J. Anderson, et al., The Effect of Cholesterol-Lowering and Antioxidant Therapy on Endothelium-Dependent Coronary Vasomotion. *New England Journal of Medicine* 1995; 332(8):488-493.
- Thomas C. Andrews, et al., Effect of Cholesterol Reduction on Myocardial Ischemia in Patients With Coronary Disease. *Circulation* 1997; 95(2):324-328.
- Roberto Antonicelli, et al., Simvastatin in the Treatment of Hypercholesterolemia in Elderly Patients. *Clinical Therapeutics* 1990; 12(2):165-171.
- Chuck Appleby, The Mouse That Roared. *Hospitals & Health Networks* 1996; 70(4):31-36.
- David Atkins, et al., Cholesterol Reduction and the Risk for Stroke in Men: A Meta-Analysis of Randomized, Controlled Trials. *Annals of Internal Medicine* 1993; 119(2):136-145.
- Rebecca G. Bakker-Arkema, et al., A Brief Review Paper of the Efficacy and Safety of Atorvastatin in Early Clinical Trials. *Atherosclerosis* 1997; 131:17-23.
- Weihang Bao, et al., Longitudinal Changes in Cardiovascular Risk From Childhood to Young Adulthood in Offspring of Parents With Coronary Artery Disease: The Bogalusa Heart Study. *Journal of the American Medical Association* 1997; 278(21):1749-1754.
- Weihang Bao, et al., Usefulness of Childhood Low-Density Lipoprotein Cholesterol Level in Predicting Adult Dyslipidemia and Other

- Cardiovascular Risks: The Bogalusa Heart Study. *Archives of Internal Medicine* 1996; 156:1315-1320.
- David S. H. Bell, A Comparison of Lovastatin, an HMG-CoA Reductase Inhibitor, with Gemfibrozil, a Fibrinic Acid Derivative, In the Treatment of Patients with Diabetic Dyslipidemia. *Clinical Therapeutics* 1995; 17(5):901-910.
- Stefano Bertolini, et al., Efficacy and Safety of Atorvastatin Compared to Pravastatin in Patients with Hypercholesterolemia. *Atherosclerosis* 1997; 130:191-197.
- David W. Bilheimer, The Lipoprotein Receptor Concept. *Drugs* 1988; 36(Suppl. 3):55-62.
- David W. Bilheimer, Therapeutic Control of Hyperlipidemia in the Prevention of Coronary Atherosclerosis: A Review of Results from Recent Clinical Trials. *American Journal of Cardiology* 1988; 62:1J-9J.
- Donald Black, et al. Cost Effectiveness of Treatment to National Cholesterol Education Panel (NCEP) Targets with HMG-CoA Reductase Inhibitors: Trial Design. *Pharmacoeconomics* 1997; 12 (2 Pt 2):278-285.
- David H. Blankenhorn, et al., Coronary Angiographic Changes with Lovastatin Therapy: The Monitored Atherosclerosis Regression Study (MARS). *Annals of Internal Medicine* 1993; 119(10):969-976.
- Conrad B. Blum, Comparison of Properties of Four Inhibitors of 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase. *American Journal of Cardiology* 1994; 73:3D-11D.
- J. Lyle Bootman, Raymond J. Townsend, and William F. McGhan, Chapter 1: Introduction to Pharmacoeconomics. Principles of Pharmacoeconomics, Second Edition, J. Lyle Bootman, Raymond J. Townsend, and William F. McGhan, eds., Harvey Whitney Books Company, Cincinnati, OH, c1996:5-18.
- Reagan H. Bradford, et al., Expanded Clinical Evaluation of Lovastatin (EXCEL) Study: Design and Patient Characteristics of a Double-Blind, Placebo-Controlled Study in Patients with Moderate Hypercholesterolemia. *American Journal of Cardiology* 1990; 66:44B-55B.

Reagan H. Bradford, et al., Expanded Clinical Evaluation of Lovastatin (EXCEL) Study Results: I. Efficacy in Modifying Plasma Lipoproteins and Adverse Event Profile in 8245 Patients With Moderate Hypercholesterolemia. *Archives of Internal Medicine* 1991; 151:43-49.

B. Greg Brown, et al., Moderate Dose, Three-Drug Therapy With Niacin, Lovastatin, and Colestipol to Reduce Low-Density Lipoprotein Cholesterol <100 mg/dl in Patients With Hyperlipidemia and Coronary Artery Disease. *American Journal of Cardiology* 1997; 80:111-115.

B. Greg Brown, et al., Types of Change in Coronary Stenosis Severity and Their Relative Importance in Overall Progression and Regression of Coronary Disease. *Annals of the New York Academy of Science*

B. Greg Brown, et al., What Benefits Can Be Derived from Treating Normocholesterolemic Patients with Coronary Artery Disease. *American Journal of Cardiology* 1995; 76:93C-97C.

Greg Brown, et al., Regression of Coronary Artery Disease as a Result of Intensive Lipid-Lowering Therapy in Men with High Levels of Apolipoprotein B. *New England Journal of Medicine* 1990; 323(19):1289-1298).

Robert Patrick Byington, et al., Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). *American Journal of Cardiology* 1995; 76:54C-59C.

Robert P. Byington, et al., Reduction in Cardiovascular Events During Pravastatin Therapy: Pooled Analysis of Clinical Events of the Pravastatin Atherosclerosis Intervention Program. *Circulation* 1995; 92(9):2419-2425.

J. Caro, et al., The West of Scotland Coronary Prevention Study: Economic Benefit Analysis of Primary Prevention with Pravastatin. *British Medical Journal* 1997; 315(7122):1577-1582.

V. F. Carr and J. C. Walker, Formulary Management in a Military Treatment Facility. *Military Medicine* 1997; 162(3):205-208.

Pak-cheung Chan, et al., Surface Expression of Low Density Lipoprotein Receptor in EBV-Transformed Lymphocytes: Characterization and Use

For Studying Familial Hypercholesterolemia. *Atherosclerosis* 1997; 131:149-160.

CHCS on-line users help menu. February, 1998.

Consumers Report. The Cholesterol Question: What You Need to Know Now. *Consumers Reports* 1996; 61(3):36-37.

Stephen J. Coons and Robert M. Kaplan, Chapter 6: Cost-Utility Analysis. Principles of Pharmacoeconomics, Second Edition. J. Lyle Bootman, Raymond J. Townsend, and William F. McGhan, eds., Harvey Whitney Books Company, Cincinnati, OH, c1996:102-126.

John Robert Crouse, et al., Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II). *American Journal of Cardiology* 1995; 75:455-459.

James E. Dalen and William S. Dalton, Commentary: Does Lowering Cholesterol Cause Cancer? *Journal of the American Medical Association* 1996; 275(1):67-69.

Giselle M. Darling, et al., Estrogen and Progestin Compared with Simvastatin for Hypercholesterolemia in Postmenopausal Women. *New England Journal of Medicine* 1997; 337(9):595-601.

Anthony Dart, et al., A Multicenter, Double-Blind, One-Year Study Comparing Safety and Efficacy of Atorvastatin Versus Simvastatin in Patients with Hypercholesterolemia. *American Journal of Cardiology* 1997; 80:39-44.

Michael H. Davidson, et al., A Comparison of Estrogen Replacement, Pravastatin, and Combined Treatment for the Management of Hypercholesterolemia in Postmenopausal Women. *Archives of Internal Medicine* 1997; 157(11):1186-1192.

Michael H. Davidson, et al., Effectiveness of Atorvastatin for Reducing Low-Density Lipoprotein Cholesterol to National Cholesterol Education Program Treatment Goals. *American Journal of Cardiology* 1997; 80(3):347-348.

Eric de Groot, et al., Effect of Pravastatin on Progression and Regression of Coronary Atherosclerosis and Vessel Wall Changes in Carotid and

- Femoral Arteries: A Report from the Regression Growth Evaluation Statin Study. *American Journal of Cardiology* 1995; 76:40C-46C.
- Vincent C. Dennis, et al., The Use of Alternate-Day Lovastatin in Hypercholesterolemic Men. *Annals of Pharmacotherapy*. 1997; 31:708-712.
- Jean-Paul Deslypere, Clinical Implications of the Biopharmaceutical Properties of Fluvastatin. *American Journal of Cardiology* 1994; 73:12D-17D.
- John R. Downs, et al., Design & Rationale of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *American Journal of Cardiology* 1997; 80:287-293.
- Stephen A. Eaker, John P. Kirscht, and Marshall H. Becker, "Understanding and Improving Patient Compliance," *Annals of Internal Medicine* 1984; 100(2): 258-269.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Journal of the American Medical Association* 1993; 269(23):3015-3023.
- John A. Farmer, et al., Comparative Effects of Simvastatin and Lovastatin in Patients with Hypercholesterolemia. *Clinical Therapeutics* 1992; 14(5):708-717.
- John A. Farmer and Antonio M. Gotto, Jr., Choosing the Right Lipid-Regulating Agent: A Guide to Selection. *Drugs* 1996; 52(5):649-661.
- Assiamira Ferrara, Elizabeth Barrett-Connor, and Jun Shan, Total, LDL, and HDL Cholesterol Decrease With Age in Older Men and Women: The Rancho Bernardo Study 1984-1994. *Circulation*. 1997; 96(1):37-43.
- David P. Foley, et al., on behalf of the FLARE study group, Prevention of Restenosis After Coronary Balloon Angioplasty: Rationale and Design of the Fluvastatin Angioplasty Restenosis (FLARE) Trial. *American Journal of Cardiology* 1994; 73:50D-61D.

Food and Drug Administration (FDA), Division of Metabolic and Endocrine Drug Products. Guidelines For The Clinical Evaluation of Lipid-Altering Agents In Adults and Children: September, 1990. Rockville, Maryland.

Philip H. Frost, et al., Coronary Heart Disease Risk Factors in Men and Women Aged 60 Years and Older: Findings From the Systolic Hypertension in the Elderly Program. *Circulation* 1996; 94(1):26-34.

Philip H. Frost, et al., Serum Lipids and Incidence of Coronary Heart Disease: Findings From the Systolic Hypertension in the Elderly Program (SHEP). *Circulation* 1996; 94(10):2381-2388.

Robert L. Frye, Clinical Reality of Lowering Total and LDL Cholesterol. *Circulation* 1997; 95 (1):306-307.

Curt D. Furberg, et al., for the Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group, Effect of Lovastatin on Early Carotid Atherosclerosis and Cardiovascular Events. *Circulation* 1994; 90(4):1679-1687.

Curt D. Furberg, et al., Pravastatin, Lipids, and Major Coronary Events. *American Journal of Cardiology* 1994; 73:1133-1134.

Curt D. Furberg, et al., for the PLAC I and PLAC II Investigators, Reduction in Coronary Events During Treatment with Pravastatin. *American Journal of Cardiology* 1995; 76:60C-63C.

Stephanie F. Gardner, et al., Combination of Low-Dose Niacin and Pravastatin Improves the Lipid Profile in Diabetic Patients Without Compromising Glycemic Control. *Annals of Pharmacotherapy* 1997; 31:677-682.

Abhimanyu Garg and Scott M. Grundy, Treatment of Dyslipidemia in Non-Insulin-Dependent Diabetes Mellitus with Lovastatin. *American Journal of Cardiology* 1988; 62:44J-49J.

William R. Garnett, A Review of Current Clinical Findings with Fluvastatin. *American Journal of Cardiology* 1996; 78(suppl 6A):20-25.

J. Michael Gaziano, Patricia R. Hebert, and Charles H. Hennekens, Cholesterol Reduction: Weighing the Benefits and Risks. *Annals of Internal Medicine* 1996; 124(10):914-918.

- Richard F. Gillum, Michael E. Mussolino, and Jennifer H. Madans, Coronary Heart Disease Incidence and Survival in African-American Women and Men: The NHANES I Epidemiologic Follow-up Study. *Annals of Internal Medicine* 1997; 127(2):111-118.
- Ronald Goldberg, et al., Comparison of the Effects of Lovastatin and Gemfibrozil on Lipids and Glucose Control in Non-Insulin-Dependent Diabetes Mellitus. *American Journal of Cardiology* 1990; 66:16B-21B.
- Edgar R. Gonzalez, Preventing Cardiovascular Atherosclerosis: Role of HMG-CoA Reductase Inhibitors. *Formulary* 1996; 31(7):582-602.
- Lawrence Gostin, Health Care Information and the Protection of Personal Privacy: Ethical and Legal Considerations. *Annals of Internal Medicine* 1997; 127 (8 Pt 2):683-690.
- A. Lawrence Gould, et al., Cholesterol Reduction Yields Clinical Benefit: A New Look at Old Data. *Circulation* 1995; 91(8):2274-2282.
- John W. Grunden and Kenneth A. Fisher, Lovastatin-Induced Rhabdomyolysis Possibly Associated with Clarithromycin and Azithromycin. *Annals of Pharmacotherapy* 1997; 31(7-8):859-863.
- Scott M. Grundy, HMG-CoA Reductase Inhibitors for Treatment of Hypercholesterolemia. *New England Journal of Medicine* 1988; 319(1):24-33.
- Scott M. Grundy, Gloria L. Vega, and Abhimanyu Garg, Use of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors in Various Forms of Dyslipidemia. *American Journal of Cardiology* 1990; 66:31B-38B.
- Zafar Hakim, Jerome Pierson, and Deva S. Pathak, A Proposed Model for Conducting Institutional-Specific Cost-Effectiveness Analysis: A Case Study of Lipid-Lowering Agents. *Pharmacy Practice and Management Quarterly* 1996; 16(1):79-97.
- Malini Haria and Donna McTavish, Pravastatin: A Reappraisal of its Pharmacological Properties and Clinical Effectiveness in the Management of Coronary Heart Disease. *Drugs* 1997; 53(2):299-336.

- Patricia R. Hebert, et al., Cholesterol Lowering With Statin Drugs, Risk of Stroke, and Total Mortality. *Journal of the American Medical Association* 1997; 278(4):313-321.
- Patricia R. Hebert, J. Michael Gaziano, and Charles H. Hennekens, An Overview of Trials of Cholesterol Lowering and Risk of Stroke. *Archives of Internal Medicine* 1995; 155(1):50-55.
- Therese M. Heinonen, et al., The Lipid-Lowering Effects of Atorvastatin, a New HMG-CoA Reductase Inhibitor: Results of a Randomized, Double-Masked Study. *Clinical Therapeutics* 1996; 18(5):853-863.
- J. Alan Herd, et al., Baseline Characteristics of Subjects in the Lipoprotein and Coronary Atherosclerosis Study (LCAS) with Fluvastatin. *American Journal of Cardiology* 1994; 73:42D-49D.
- J. Alan Herd, et al., Effects of Fluvastatin on Coronary Atherosclerosis in Patients With Mild to Moderate Cholesterol Elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). *American Journal of Cardiology* 1997; 80:278-286.
- Wendy Herr, Data Integration: HFMA Study Findings. *Healthcare Financial Management* September 1996:52-56.
- D. Hilleman, et al., Pharmacoeconomic Assessment of HMG-CoA Reductase Inhibitor Therapy: An Analysis Based on the CURVES Study. (Poster presentation at ISPOR Lipid Conference in Orlando, FL; November 4-6, 1997).
- Kathy Hitchens, Improving Cholesterol Compliance. *American Druggist* January 1996:34-37.
- Jeffrey M. Hoeg, Evaluating Coronary Heart Disease Risk: Tiles in the Mosaic. *Journal of the American Medical Association* 1997; 277(17):1387-1390.
- Ingar Holme, An Analysis of Randomized Trials Evaluating the Effect of Cholesterol Reduction on Total Mortality and Coronary Heart Disease Incidence. *Circulation* 1990; 82(6):1916-1924.
- Ingar Holme, Cholesterol Reduction and Its Impact on Coronary Artery Disease and Total Mortality. *American Journal of Cardiology* 1995; 76:10C-17C.

- H. Honjo, et al., Menopause and Hyperlipidemia: Pravastatin Lowers Lipid Levels Without Decreasing Endogenous Estrogens. *Clinical Therapeutics* 1992; 14(5):699-707.
- G. Howard, et al., Cigarette Smoking and Progression of Atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study. *Journal of the American Medical Association* 1998; 279(2):119-124.
- D. Hunninghake, LDL-Cholesterol as a Determinant of Coronary Heart Disease. *Clinical Therapeutics* 1990; 12(5):370-375.
- Osamah Hussein, et al., Reduced Susceptibility of Low Density Lipoprotein (LDL) to Lipid Peroxidation After Fluvastatin Therapy is Associate with the Hypocholesterolemic Effect of the Drug and its Binding to the LDL. *Atherosclerosis* 1997; 128:11-18.
- Jussi K. Huttunen, et al., Helsinki Heart Study: New Perspectives in the Prevention of Coronary Heart Disease. *Drugs* 1988; 36(Suppl. 3):32-36.
- Hajime Ide, et al., Effects of Simvastatin, an HMG-CoA Reductase inhibitor, on Plasma Lipids and Steroid Hormones. *Clinical Therapeutic* 1990; 12(5):410-420.
- D. Roger Illingworth, How Effective Is Drug Therapy in Heterozygous Familial Hypercholesterolemia? *American Journal of Cardiology* 1993; 72:54D-58D.
- D. Roger Illingworth and Sandra Bacon, Hypolipidemic Effects of HMG-CoA Reductase Inhibitors in Patients with Hypercholesterolemia. *American Journal of Cardiology* 1987; 60:33G-42G.
- D. Roger Illingworth, Lipid-Lowering Drugs: An Overview of Indications and Optimum Use. *Drugs* 1987; 33:259-279.
- D. Roger Illingworth, An Overview of Lipid-Lowering Drugs. *Drugs* 1988; 36(Suppl. 3):63-71.
- D. Roger Illingworth and Jonathan A. Tobert, A Review of Clinical Trials Comparing HMG-CoA Reductase Inhibitors. *Clinical Therapeutics* 1994; 16(3):366-385.

- D. Roger Illingworth, Therapeutic Use of Lovastatin in the Treatment of Hypercholesterolemia. *Clinical Therapeutics* 1994; 16(1):2-26.
- Carlos Iribarren, et al., Twelve-Year Trends in Cardiovascular Disease Risk Factors in the Minnesota Heart Survey: Are Socioeconomic Differences Widening? *Archives of Internal Medicine* 1997; 157(8):873-881.
- H. Iso, et al., for the MRFIT Research Group., Serum Cholesterol Levels and Six-Year Mortality From Stroke in 350,977 Men Screened for the Multiple Risk Factor Intervention Trial. *New England Journal of Medicine* 1989; 320(14):904-910.
- Terry A. Jacobson, Cost-Effectiveness of 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitor Therapy in the Managed Care Era. *American Journal of Cardiology* 1996; 78(6A):32-41.
- Terry A. Jacobson and Louis F. Amorosa, Combination Therapy with Fluvastatin and Niacin in Hypercholesterolemia: A Preliminary Report on Safety. *American Journal of Cardiology* 1994; 73:25D-29D.
- Magnus Johannesson, et al., for the Scandinavian Simvastatin Survival Study Group, Cost Effectiveness of Simvastatin Treatment to Lower Cholesterol Levels in Patients with Coronary Heart Disease. *New England Journal of Medicine* 1997; 336(5):332-336.
- Clifford L. Johnson, et al., Declining Serum Total Cholesterol Levels Among US Adults: The National Health and Nutrition Examination Surveys. *Journal of the American Medical Association* 1993; 269(23):3002-3008.
- Leonard A. Jokubaitis, Updated Clinical Safety Experience with Fluvastatin. *American Journal of Cardiology* 1994; 73:18D-24D.
- Peter H. Jones, Lovastatin and Simvastatin Prevention Studies. *American Journal of Cardiology* 1990; 66:39B-43B.
- Peter H. Jones and Antonio M. Gotto, Jr., Extending the Benefit of Lipid-Regulating Therapy to Primary Prevention. *American Journal of Cardiology* 1995; 76:118C-121C.
- J. Wouter Jukema, et al., Effects of Lipid Lowering by Pravastatin on Progression and Regression of Coronary Artery Disease in Symptomatic Men With

Normal to Moderately Elevated Serum Cholesterol Levels: The Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 1995; 91(10):2528-2540.

M. Ilyas Kamboh, et al., Plasma Apolipoprotein A-I, Apolipoprotein B, and Lipoprotein(a) Concentrations in Normoglycemic Hispanics and Non-Hispanic Whites from the San Luis Valley, Colorado. *American Journal of Epidemiology* 1997; 146(12):1011-1018.

William B. Kannel, et al., Efficacy and Tolerability of Lovastatin in a Six-Month Study: Analysis by Gender, Age and Hypertensive Status. *American Journal of Cardiology* 1990; 66:1B-10B.

William B. Kannel, et al., Factors of Risk in the Development of Coronary Heart Disease - Six-Year Follow-up Experience: The Framingham Study. *Annals of Internal Medicine* 1961; 55(1):33-50.

William B. Kannel, Range of Serum Cholesterol Values in the Population Developing Coronary Artery Disease. *American Journal of Cardiology* 1995; 76:69C-77C.

Klaus U. Kirchgassler, Julia Schiffner-Rohe and Ursula Stahlheber, Cost Effectiveness of Micronised Fenofibrate and Simvastatin in the Short Term Treatment of Type IIa and Type IIb Hyperlipidemia. *Pharmacoeconomics* 1997; 12(2 Pt 2):237-246.

John Kjekshus and Terje R. Pedersen, for the Scandinavian Simvastatin Survival Study Group, Reducing the Risk of Coronary Events: Evidence from the Scandinavian Simvastatin Survival Study (4S). *American Journal of Cardiology* 1995; 76:64C-68C.

Robert H. Knopp, Jiri J. Frolich, Efficacy and Safety of Fluvastatin in Patients with Non-Insulin-Dependent Diabetes Mellitus and Hyperlipidemia: Preliminary Report. *American Journal of Cardiology* 1994; 73:39D-41D.

Sheldon X. Kong, et al., Efficacy of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors in the Treatment of Patients with Hypercholesterolemia: A Meta-Analysis of Clinical Trials. *Clinical Therapeutics* 1997; 19(4):778-797.

- Lisa Korman and Lydia Borysiuk, Replacing Lovastatin with Pravastatin: Effect on Serum Lipids and Costs. *American Journal of Health-System Pharmacy* 1995; 52(10):1078-1082.
- Darwin R. Labarthe, et al., Development of Cardiovascular Risk Factors From Ages 8 to 18 in Project HeartBeat!: Study Design and Patterns in Plasma Total Cholesterol Concentration. *Circulation* 1997; 95:2636-2642.
- Benoit Lamarche, et al., Apolipoprotein A-I and B Levels and the Risk of Ischemic Heart Disease During a Five-Year Follow-up of Men in the Quebec Cardiovascular Study. *Circulation* 1996; 94(3):273-278.
- Benoit Lamarche, et al., Small, Dense Low-Density Lipoprotein Particles as a Predictor of the Risk of Ischemic Heart Disease in Men: Prospective Results From the Quebec Cardiovascular Study. *Circulation* 1997; 95(1):69-75.
- Paul C. Langley, The Future of Pharmacoeconomics: A Commentary. *Clinical Therapeutics* 1997;19(4):762-769.
- John C. LaRosa, Unresolved Issues in Early Trials of Cholesterol Lowering. *American Journal of Cardiology* 1995; 76:5C-9C.
- Lon N. Larson, Chapter 3: Cost Determination and Analysis. Principles of Pharmacoeconomics, Second Edition. J. Lyle Bootman, Raymond J. Townsend, and William F. McGhan, eds., Harvey Whitney Books Company, Cincinnati, OH, c1996:44-59.
- Andrew P. Lea and Donna McTavish, Atorvastatin: A Review of its Pharmacology and Therapeutic Potential in the Management of Hyperlipidaemias. *Drugs* 1997; 53(5):828-847.
- A. L. Lehninger, D. L. Nelson, and M. M. Cox, Chapter 20 - Lipid Biosynthesis. Principles of Biochemistry, Second Edition. Worth Publishers, New York, NY, c1993:674-682.
- Eran Leitersdorf, Gender-Related Response to Fluvastatin in Patients with Heterozygous Familial Hypercholesterolaemia. *Drugs* 1994; 47(Suppl. 2):54-63.

W. Leonhardt, et al., Effects of Fluvastatin Therapy on Lipids, Antioxidants, Oxidation of Low Density Lipoproteins and Trace Metals. *European Journal of Clinical Pharmacology* 1997; 53(1):65-69.

Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial Results: 1. Reduction in Incidence of Coronary Heart Disease. *Journal of the American Medical Association* 1984; 251(3):351-364.

The Lipid Study Group, Design Features and Baseline Characteristics of the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) Study: A Randomized Trial in Patients with Previous Acute Myocardial Infarction and/or Unstable Angina Pectoris. *American Journal of Cardiology* 1995; 76:474-479.

The Lovastatin Study Group IV. A Multicenter Comparison of Lovastatin and Probucol for Treatment of Severe Primary Hypercholesterolemia. *American Journal of Cardiology* 1990; 66:22B-30B.

MAAS Investigators. Effect of Simvastatin on Coronary Atheroma: The Multicentre Anti-Atheroma Study (MAAS). *Lancet* 1994; 344(8923):633-638.

Vincent Maher, et al., Primary Prevention of Coronary Heart Disease: What Has WOSCOPS Told Us and What Questions Remain? *Drugs* 1997; 54(1):1-8.

Pier L. Malini, et al., Simvastatin Versus Pravastatin: Efficacy and Tolerability in Patients with Primary Hypercholesterolemia. *Clinical Therapeutics* 1991; 13(4):500-509.

Geraldine Mantell, Theresa Burke and Joan Staggers, Extended Clinical Safety Profile of Lovastatin. *American Journal of Cardiology* 1990; 66:11B-15B.

Alan O. Marcus, Rationale for Effective Treatment of Hypercholesterolemia. *American Journal of Cardiology* 1996; 78(suppl 6A):4-12.

Leon L. Martens and Remi Guilbert, Cost-Effectiveness Analysis of Lipid-Modifying Therapy in Canada: Comparison of HMG-CoA Reductase

Inhibitors in the Primary Prevention of Coronary Heart Disease. *Clinical Therapeutics* 1994; 16(6):1052-1062.

James P. McCormick, Marc Levine, and Robert E. Rango, Primary Prevention of Heart Disease and Stroke: A Simplified approach to Estimating Risk of Events and Making Drug Treatment Decisions. *Canadian Medical Association Journal* 1997; 157(4):422-428.

Lisa S. McCormick, et al., Rationale, Design, and Baseline Characteristics of a Trial Comparing Aggressive Lipid Lowering with Atorvastatin Versus Revascularization Treatments (AVERT). *American Journal of Cardiology* 1997; 80:1130-1133.

Clement J. McDonald, et al. A Framework for Capturing Clinical Data Sets from Computerized Sources. *Annals of Internal Medicine* 1997; 127(8 Pt 2):675-682.

Mary McGrae McDermott, Brian Schmitt, and Elisabeth Wallner, Impact of Medication Nonadherence on Coronary Heart Disease Outcomes: A Critical Review. *Archives of Internal Medicine* 1997; 157:1921-1929.

Ruth McPherson, Comparison of the Short-Term Efficacy and Tolerability of Lovastatin and Pravastatin in the Management of Primary Hypercholesterolemia. *Clinical Therapeutics* 1992; 14(2):276-291.

Braxton D. Mitchell, et al., Genetic and Environmental Contributions to Cardiovascular Risk Factors in Mexican Americans: The San Antonio Family Heart Study. *Circulation* 1996; 94(9):2159-2170.

Mohammed H. Moghadasian, Bruce M. McManus, and Jiri J. Frohlich, Homocyst(e)ine and Coronary Artery Disease: Clinical Evidence and Genetic and Metabolic Background. *Archives of Internal Medicine* 1997; 157:2299-2308.

Shigeto Morimoto, et al., Long-Term Effects of Pravastatin on Serum Lipid Levels in Elderly Patients with Hypercholesterolemia. *Clinical Therapeutics* 1994; 16(5):793-803.

Brenda R. Motheral and Kathleen A. Fairman, The Use of Claims Databases for Outcomes Research: Rationale, Challenges, and Strategies. *Clinical Therapeutics* 1997; 19(2):346-366.

Matthew F. Muldoon, Stephen B. Manuck, and Karen A. Matthews, Lowering Cholesterol Concentrations and Mortality: A Quantitative Review of Primary Prevention Trials. *British Medical Journal* 1990; 301:309-314.

The Multiple Risk Factor Intervention Trial Research Group,. Mortality After 16 Years for Participants Randomized to the Multiple Risk Factor Intervention Trial. *Circulation* 1996; 94(5):946-951.

Jun Muramatsu, et al., Hemodynamic Changes Associated with Reduction in Total Cholesterol by Treatment with the HMG-CoA Reductase Inhibitor Pravastatin. *Atherosclerosis* 1997; 130:179-182.

Eleonora Muratti, Tim K. Peters and Eran Leitersdorf, Fluvastatin in Familial Hypercholesterolemia: A Cohort Analysis of the Response to Combination Treatment. *American Journal of Cardiology* 1994; 73:30D-38D.

John Murphy and Gregor Coster, Issues in Patient Compliance. *Drugs* 1997; 54(6):797-800.

Rossitea Naoumova, et al., Prolonged Inhibition of Cholesterol Synthesis Explains the Efficacy of Atorvastatin. *Journal of Lipid Research* 1997; 38(7):1496-1500.

Y. Narita, et al., Increase or Decrease of HDL-Cholesterol Concentrations During Pravastatin Treatment Depending on the Pre-Treatment HDL Cholesterol Levels. *European Journal of Clinical Pharmacology* 1997; 52(6):461-463.

David T. Nash, Meeting National Cholesterol Education Goals in Clinical Practice - A Comparison of Lovastatin and Fluvastatin in Primary Prevention. *American Journal of Cardiology* 1996; 78(suppl 6A):26-31.

Mohamad Navab, et al., Pathogenesis of Atherosclerosis. *American Journal of Cardiology* 1995; 76:18C-23C.

Paul Nestel, et al., A Comparative Study of the Efficacy of Simvastatin and Gemfibrozil in Combined Hyperlipoproteinemia: Prediction of Response by Baseline Lipids, Apo E Genotype, Lipoprotein(a) and Insulin. *Atherosclerosis* 1997; 129:231-239.

- Thomas B. Newman and Stephen B. Hulley, Carcinogenicity of Lipid-Lowering Drugs. *Journal of the American Medical Association* 1996; 275(1):55-60.
- Harri Niinikoski, et al., Prospective Randomized Trial of Low-Saturated-Fat, Low-Cholesterol Diet During the First 3 Years of Life: The STRIP Baby Project. *Circulation* 1996; 94:1386-1393.
- Gerard O'Driscoll, Danny Green and Roger Taylor, Simvastatin, and HMG-Coenzyme A Reductase Inhibitor, Improves Endothelial Function Within 1 Month. *Circulation* 1997; 95(5):1126-1131.
- Gary J. Okano, et al., Patterns of Antihypertensive Use Among Patients in the US Department of Defense Database Initially prescribed an ACE Inhibitor or Calcium Channel Blocker. *Clinical Therapeutics* 1997; 19(6):1433-1445.
- M. F. Oliver, Doubts About Preventing Coronary Heart Disease: Multiple Interventions in Middle Aged Men May Do More Harm Than Good. *British Medical Journal* 1992; 304:393-394.
- M. F. Oliver, Might Treatment of Hypercholesterolaemia Increase Non-Cardiac Mortality? *Lancet* 1991; 337:1529-1531.
- Henry Y. Pan, et al., Comparative Efficacy of Once-Daily Versus Twice-Daily Pravastatin in Primary Hypercholesterolemia. *Clinical Therapeutics* 1991; 13(3):368-372.
- Terje R. Pedersen, et al., Safety and Tolerability of Cholesterol Lowering With Simvastatin During 5 Years in the Scandinavian Simvastatin Survival Study. *Archives of Internal Medicine* 1996; 156:2085-2092.
- T. K. Peters, E. N. Muratti, M. Mehra, Efficacy and Safety of Fluvastatin in Women with Primary Hypercholesterolaemia. *Drugs* 1994; 47(Suppl. 2):64-72.
- Patricia A. Peyser, Genetic Epidemiology of Coronary Artery Disease. *Epidemiologic Reviews* 1997; 19(1):80-90.
- Marc A. Pfeffer, et al., Cholesterol and Recurrent Events: A Secondary Prevention Trial for Normolipidemic Patients. *American Journal of Cardiology* 1995; 76:98C-106C.

Pharmacoeconomic Center, PEC Update. 16 October 1995; 96(01):1-A19.

Amos Pines, Yoran Levo and Daniel Ayalon, Hormone-Replacement Therapy Compared with Simvastatin for Postmenopausal Women with Hypercholesterolemia. *New England Journal of Medicine* 1998; 338(1):63-64.

Kimmo V. K. Porkka, et al., Trends in Serum Lipid Levels during 1980-1992 in Children and Young Adults: The Cardiovascular Risk in Young Finns Study. *American Journal of Epidemiology* 1997; 146(1):64-77.

The Pravastatin Multinational Study Group for Cardiac Risk Patients, Effects of Pravastatin in Patients with Serum Total Cholesterol Levels from 5.2 to 7.8 mmol/liter (200 to 300 mg/dl) Plus Two Additional Atherosclerotic Risk Factors. *American Journal of Cardiology* 1993; 72:1031-1037.

Jeffrey L. Probstfield, et al., for the ACAPS Research Group. Results of the Primary Outcome Measure and Clinical Events from the Asymptomatic Carotid Artery Progression Study. *American Journal of Cardiology* 1995; 75:47C-53C.

Prospective Studies Collaboration, Cholesterol, Diastolic Blood Pressure, and Stroke: 13,000 Strokes in 450,000 People in 45 Prospective Cohorts. *Lancet* 1995; 346(8988):1647-1653.

Frederick J. Raal, et al., Statin Therapy in a Kindred with Both Apolipoprotein B and Low Density Lipoprotein Receptor Gene Defects. *Atherosclerosis* 1997; 129:97-102.

B. M. Rifkind, The Lipid Research Clinics Coronary Primary Prevention Trial. *Drugs* 1986; 31(Suppl. 1):53-60.

Joseph P. Rindone, et al., Changes in Serum Lipids When Fluvastatin is Substituted for Lovastatin in the Same Doses. *American Journal of Cardiology* 1997; 80(3):348-349.

Robert S. Rosenson, Beyond Low-Density Lipoprotein Cholesterol: A Perspective on Low High-Density Lipoprotein Disorders and Lp(a) Lipoprotein Excess. *Archives of Internal Medicine* 1996; 156:1278-1284.

Jacques E. Rossouw, Lipid-Lowering Interventions in Angiographic Trials. *American Journal of Cardiology* 1995; 76:86C-92C.

Jacques E. Rossouw, Barry Lewis, and Basil M. Rifkind, The Value of Lowering Cholesterol After Myocardial Infarction. *New England Journal of Medicine* 1990; 323(16):1112-1119.

Plans Rubio, Cost-Effectiveness of Dietary Treatment of Hypercholesterolemia in Spain. *Public Health* 1997; 111(1):33-40.

Frank M. Sacks, et al, for the Harvard Atherosclerosis Reversibility Project (HARP) Group, Effect on Coronary Atherosclerosis of Decrease in Plasma Cholesterol Concentrations in Normocholesterolaemic Patients. *Lancet* 1994; 344(8931):1182-1186.

Frank M. Sacks, et al., The Effect of Pravastatin on Coronary Events after Myocardial Infarction in Patients with Average Cholesterol Levels. *New England Journal of Medicine* 1996; 335(14):1001-1009.

Frank M. Sacks, et al., The Influence of Pretreatment Low Density Lipoprotein Cholesterol Concentrations on the Effect of Hypocholesterolemic Therapy on Coronary Atherosclerosis in Angiographic Trials. *American Journal of Cardiology* 1995; 76:78C-85C.

Rakesh Sahni, et al., Prevention of Restenosis by Lovastatin After Successful Coronary Angioplasty. *American Heart Journal* 1991; 121(6, part 1):1600-1608.

Keifiro Saku, Jun Sasaki, and Kikuo Arakawa, Low-Dose Effect of Simvastatin (MK-733) on Serum Lipids, Lipoproteins, and Apolipoproteins in Patients with Hypercholesterolemia. *Clinical Therapeutics* 1989; 11(2):247-257.

Riitta Salonen, et al., Kuopio Atherosclerosis Prevention Study (KAPS): A Population-Based Primary Preventive Trial of the Effect of LDL Lowering on Atherosclerotic Progression in Carotid and Femoral Arteries. *Circulation* 1995; 92(7):1758-1764.

Riitta Salonen, et al., The Kuopio Atherosclerosis Prevention Study (KAPS): Effects of Pravastatin Treatment on Lipids, Oxidation Resistance of Lipoproteins, and Atherosclerotic Progression. *American Journal of Cardiology* 1995; 76:34C-39C.

- Scandinavian Simvastatin Survival Study Group, Baseline Serum Cholesterol and Treatment Effect in the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1995; 345(8960):1274-1275.
- Scandinavian Simvastatin Survival Study Group, Randomized Trial of Cholesterol Lowering in 4444 Patients with Coronary Heart Disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344(8934):1383-1389.
- Marieke Dekker Schoen, Lipid Management: An Opportunity for Pharmacy Service. *Journal of the American Pharmaceutical Association* 1996; NS36(10):609-619.
- Helmut G. Schrott, et al., Adherence to National Cholesterol Education Program Treatment Goals in Postmenopausal Women With Heart Disease: The Heart and Estrogen/Progestin Replacement Study (HERS). *Journal of the American Medical Association* 1997; 277(16):1281-1286.
- Andrew P. Selwyn, Scott Kinlay, and Peter Ganz, Atherogenesis and Ischemic Heart Disease. *American Journal of Cardiology* 1997; 80(8B):3H-7H.
- Christopher T. Sempos, et al., Prevalence of High Blood Cholesterol Among US Adults: An Update Based on Guidelines From the Second Report of the National Cholesterol Education Program Adult Treatment Panel. *Journal of the American Medical Association* 1993; 269(23):3009-3014.
- Charles L. Shear, et al., Expanded Clinical Evaluation of Lovastatin (EXCEL) Study Results: Effect of Patient Characteristics on Lovastatin-Induced Changes in Plasma Concentrations of Lipids and Lipoproteins. *Circulation* 1992; 85:1293-1303.
- SHEP Cooperative Research Group, Prevention of Stroke by Antihypertensive Drug Treatment in Older Persons With Isolated Systolic Hypertension: Final Results of the Systolic Hypertension in the Elderly Program (SHEP). *Journal of the American Medical Association* 1991; 265(24):3255-3264.
- James Shepherd, et al., Prevention of Coronary Heart Disease with Pravastatin in Men with Hypercholesterolemia. *New England Journal of Medicine* 1995; 333(20):1301-1307.

- James Shepherd, for The West of Scotland Coronary Prevention Study Group, The West of Scotland Coronary Prevention Study: A Trial of Cholesterol Reduction in Scottish Men. *American Journal of Cardiology* 1995; 76:113C-117C.
- R. John Simes, on behalf of the PPP and CTT Investigators, Prospective Meta-Analysis of Cholesterol-Lowering Studies: The Prospective Pravastatin Pooling (PPP) Project and the Cholesterol Treatment Trialists (CTT) Collaboration. *American Journal of Cardiology* 1995; 76:122C-126C.
- W. Robert Simons and M. Eugene Smith, Health Economics and Outcomes Research with Retrospective Data. *Clinical Therapeutics* 1994; 16(6):1063-1067.
- Eve E. Slater and James S. MacDonald, Mechanism of Action and Biological Profile of HMG CoA Reductase Inhibitors: A New Therapeutic Alternative. *Drugs* 1988; 36(Suppl. 3):72-82.
- George D. Smith and Juha Pekkanen, For Debate: Should There Be a Moratorium on the Use of Cholesterol Lowering Drugs? *British Medical Journal* 1992; 304:431-434.
- Sidney C. Smith, Review of Recent Clinical Trials of Lipid Lowering in Coronary Artery Disease. *American Journal of Cardiology* 1997; 80(8B):10H-13H.
- Marshall E. Spearman, et al., Cost-Effectiveness of Initial Therapy with 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors to Treat Hypercholesterolemia in a Primary Care Setting of a Managed-Care Organization. *Clinical Therapeutics* 1997; 19(3):582-602.
- SPSS Inc. SPSS® Base 7.5 for Windows User's Guide. SPSS Inc., Chicago, IL, c1997:73-76.
- SPSS Inc. SPSS® Base 7.5 for Windows User's Guide. SPSS Inc., Chicago, IL, c1997:77.
- J. Stamler, et al., for the MRFIT Research Group. Relationship to Blood Pressure of Combinations of Dietary Macronutrients: Findings of the Multiple Risk Factor Intervention Trial (MRFIT). *Circulation* 1996; 94(10):2417-2423.

- Robert M. Stark, Review of the Major Intervention Trials of Lowering Coronary Artery Disease Risk Through Cholesterol Reduction. *American Journal of Cardiology* 1996; 78(Suppl. 6A):13-19.
- E. A. Stein, Drug and Alternative Therapies for Hyperlipidemia. *Atherosclerosis* 1994; 108(suppl.):S105-S116.
- James H. Stein and Robert S. Rosenson, Lipoprotein Lp(a) Excess and Coronary Heart Disease. *Archives of Internal Medicine* 1997; 157:1170-1176.
- Daniel Steinberg, Lewis A. Conner Memorial Lecture: Oxidative Modification of LDL and Atherogenesis. *Circulation* 1997; 95(4):1062-1071.
- G. Steiner, Diabetes and Atherosclerosis: Metabolic Links. *Drugs* 1988; 36(Suppl. 3):22-26.
- Brian L. Strom, Chapter 23: Other Approaches to Pharmacoepidemiology Studies. Pharmacoepidemiology, Second edition. Brian L. Strom, ed., c1994:323-335.
- Brian L. Strom, Chapter 24: How Should One Perform Pharmacoepidemiology Studies? Choosing Among the Available Alternatives. Pharmacoepidemiology, Second Edition. Brian L. Strom, ed., c1994:337-350.
- H. Robert Superko, Beyond LDL Cholesterol Reduction. *Circulation* 1996; 94(10):2351-2354.
- H. Robert Superko, R. M. Krauss, and C. DiRicco, Effect of Fluvastatin on Low-Density Lipoprotein Peak Particle Diameter. *American Journal of Cardiology* 1997; 80:78-81.
- Anna E. Sweaney, et al., Effects of Simvastatin Versus Gemfibrozil on Lipids and Glucose Control in Patients with Non-Insulin-Dependent Diabetes Mellitus. *Clinical Therapeutics* 1995; 17(2):186-203.
- Mikko Syvanne and Marja-Riitta Taskinen, Lipids and Lipoproteins As Coronary Risk Factors in Non-Insulin-Dependent Diabetes Mellitus. *Lancet* 1997; 350(Supl. 1):20-23.
- Robert Talbert, Personal communication. April 1, 1998.

- L. Tenkanen, M. Manttari, and V. Manninen, Some Coronary Risk Factors Related to the Insulin Resistance Syndrome and Treatment With Gemfibrozil. *Circulation* 1995; 92:1779-1785.
- Gilbert R. Thompson, What Targets Should Lipid-Modulating Therapy Achieve to Optimize the Prevention of Coronary Heart Disease? *Atherosclerosis* 1997; 131:1-5.
- Matti J. Tikkanen and Kalevi Pyorala, Cholesterol Reduction and Coronary Artery Disease: An Overview of Clinical Trials up to 1986. *Drugs* 1988; 36(Suppl. 3):27-31.
- Matti J. Tikkanen, et al., Comparison Between Lovastatin and Gemfibrozil in the Treatment of Primary Hypercholesterolemia: The Finnish Multicenter Study. *American Journal of Cardiology* 1988;62:35J-43J.
- Jonathan A. Tobert, Efficacy and Long-Term Adverse Effect Pattern of Lovastatin. *American Journal of Cardiology* 1988; 62:28J-34J.
- Andrew M. Tonkin, for the LIPID Study Group, Management of the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study after the Scandinavian Simvastatin Survival Study (4S). *American Journal of Cardiology* 1995; 76:107C-112C.
- S. Vitols, B. Angelin and G. Juliusson, Simvastatin Impairs Mitogen-Induced Proliferation of Malignant B-Lymphocytes from Humans - In Vitro and In Vivo Studies. *Lipids* 1997; 32(3):255-262.
- David Waters, et al., Effects of Cigarette Smoking on the Angiographic Evolution of Coronary Atherosclerosis: A Canadian Coronary Atherosclerosis Intervention Trail (CCAIT) Substudy. *Circulation* 1996; 94:614-621.
- David Waters, et al., Effects of Monotherapy With an HMG-CoA Reductase Inhibitor on the Progression of Coronary Atherosclerosis as Assessed by Serial Quantitative Arteriography: The Canadian Coronary Atherosclerosis Intervention Trial. *Circulation* 1994; 89:959-968.
- William S. Weintraub, et al., Lack of Effect of Lovastatin on Restenosis After Coronary Angioplasty. *New England Journal of Medicine* 1994; 331(20):1331- 1337.

- The West of Scotland Coronary Prevention Study Group, A Coronary Primary Prevention Study of Scottish Men Aged 45-64 Years: Trial Design. *Journal of Clinical Epidemiology* 1992; 45(8):849-860.
- Annelies W. E. Weverling-Rijnsburger, et al., Total Cholesterol and Risk of Mortality in the Oldest Old. *Lancet* 1997; 350(9085):1119-1123.
- P. W. F. Wilson, et al. Cumulative Effects of High Cholesterol Levels, High Blood Pressure, and Cigarette Smoking on Carotid Stenosis. *New England Journal of Medicine* 1997; 337(8):516-522.
- Gregory R. Wise and Trang T. Schultz, Hyperlipidemia: When Does Treatment Make a Difference? *Post Graduate Medicine* 1996; 100(1):138-149.
- Daniel Yeshurun, et al., Treatment of Severe, Resistant Familial Combined Hyperlipidemia with a Bezafibrate-Lovastatin Combination. *Clinical Therapeutics* 1993; 15(2):355-363.
- Hiroshi Yoshida, et al., Effects of Low-Dose Simvastatin on Cholesterol Levels, Oxidative Susceptibility, and Antioxidant Levels of Low-Density Lipoproteins on Patients with Hypercholesterolemia: A Pilot Study. *Clinical Therapeutics* 1995; 17(3):379-389.
- Jose L. Zambrana, et al., Comparison of Bezafibrate Versus Lovastatin for Lowering Plasma Insulin, Fibrinogen, and Plasminogen Activator Inhibitor-1 Concentrations in Hyperlipemic Heart Transplant Patients. *American Journal of Cardiology* 1997; 80:836-840.

Vita

Cynthia Leah Lee-Ziegler was born in Greenville, South Carolina, on July 6, 1954. She is the daughter of Lucy Maxine Manness Chapman and John Earnest Chapman. After graduating from Emil R. Buchser High School, Santa Clara, California, in June 1972, Cynthia served in the United States Army for two years. She started in pharmacy school at the University of Cincinnati, Cincinnati, Ohio, in October of 1974 and graduated with a Bachelor of Science degree in Pharmacy in June 1979. She practiced as a registered pharmacist in the Detroit, Michigan, and Houston, Texas, areas until becoming a commissioned officer in the United States Air Force in August 1990. She served at the Wilford Hall Medical Center at Lackland Air Force Base, San Antonio, Texas, from August 1990 through August 1996. Cynthia received her Master of Arts degree in Health Services and Computer and Information Resource Management from Webster University, headquartered in St. Louis, Missouri, in July 1992. She entered the University of Texas at Austin in August 1996.

Permanent address: 8723 Prince Heights, San Antonio, Texas 78250

This dissertation was typed by the author.